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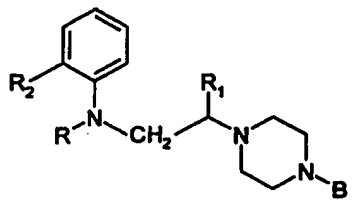

(I)

(57) Abstract

1-(N-phenylaminoalkyl)-piperazine derivatives of formula (I), (R = H, alkyl-CO, cycloalkyl-CO, substituted cycloalkyl-CO or monocyclic heteroaryl-CO; R_1 = H or lower alkyl; R_2 = halogen, alkoxy, phenoxy, NO_2, CN, acyl, NH_2, NH(acyl), alkyl-SO_2NH, alkoxycarbonyl, NH_2CO, (alkyl)NHCO, (alkyl)$_2$NCO, (acyl)NHCO, CF_3 or polyfluoroalkoxy; B = benzyl or mono- or bicyclic aryl or heteroaryl, all optionally substituted) bind to $5HT_{1A}$ receptors and are useful for the treatment of neuromuscular dysfunctions of the lower urinary tract. The use of these compounds for the preparation of a medicament for this treatment is claimed, and some of the compounds (with restricted B values) are claimed per se.

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1-(N-PHENYLAMINOALKYL)-PIPERAZINE DERIVATIVES SUBSTITUTED AT POSITION 2 OF THE PHENYL RING

FIELD OF THE INVENTION

This invention relates to 1-(N-phenylaminoalkyl)-piperazine derivatives substituted at position 2 of the phenyl ring, to pharmaceutical compositions containing them and to uses for such derivatives and compositions.

BACKGROUND OF THE INVENTION

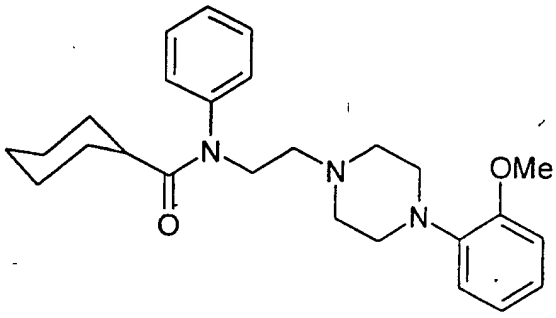
In mammals, micturition (urination) is a complex process that requires the integrated actions of the bladder, its internal and external sphincters, the musculature of the pelvic floor, and neurological control over these muscles at three levels (in the bladder wall or sphincter itself, in the autonomic centres of the spinal cord, and in the central nervous system at the level of the pontine micturition centre (PMC) in the brainstem (pons) under the control of cerebral cortex) (De Groat, *Neurobiology of Incontinence*, (Ciba Foundation Symposium 151:27, 1990). Micturition results from contraction of the detrusor muscle, which consists of interlacing smooth muscle fibres under parasympathetic autonomic control from the sacral spinal cord. A simple voiding reflex is formed by sensory nerves for pain, temperature, and distension that run from the bladder to the sacral cord. However, sensory tracts from the bladder also reach the PMC, resulting in the generation of nerve impulses that normally suppress the sacral spinal reflex arc controlling bladder emptying. Thus, normal micturition is initiated by voluntary suppression of cortical inhibition of the reflex arc and by relaxation of the muscles of the pelvic floor and the external sphincter. Finally, the detrusor muscle contracts and voiding occurs.

Abnormalities of lower urinary tract function, e.g., dysuria, incontinence, and enuresis, are common in the general population. Dysuria includes urinary frequency, nocturia, and urgency, and may be caused by cystitis, prostatitis or benign prostatic hypertrophy (BPH) (which affects about 70% of elderly males), or by neurological disorders. Incontinence syndromes include stress incontinence, urgency incontinence, and overflow incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

Prior to the work of the present inventors, treatment of neuromuscular dysfunction of the lower urinary tract has involved administration of compounds that act directly on the bladder muscles, such as flavoxate, a spasmolytic drug (Ruffman, *J. Int.Med.Res.* 16:317, 1988) also active on the PMC (Guarneri et al., *Drugs of Today* 30:91, 1994), or anticholinergic compounds such as oxybutynin (Andersson, *Drugs* 35:477, 1988). The use of α_1-adrenergic receptor antagonists for the treatment of BPH is also common but is based on a different mechanism of action. (Lepor, *Urology*, 42:483, 1993).

However, treatments that involve direct inhibition of the pelvic musculature (including the detrusor muscle) may have unwanted side effects such as incomplete voiding or accommodation paralysis, tachycardia and dry mouth (Andersson, *Drugs* 35:477, 1988). Thus, it would be advantageous if compounds were available that act via the peripheral or central nervous system to, for example, affect the sacral spinal reflex arc and/or the PMC inhibition pathways in a manner that restores normal functioning of the micturition mechanism.

1-(N-phenyl-N-cyclohexylcarbonyl-2-aminoethyl)-4-(2-methoxyphenyl)-piperazine (compound A)



(A)

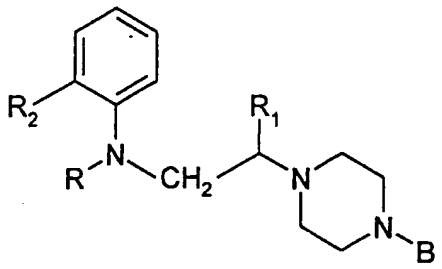
is described in GB 2263110 and is reported to be a 5-HT_{1A} receptor antagonist. It is also disclosed that it can be used for the treatment of central nervous system disorders, for example as an anxiolytic agent in the treatment of anxiety.

The compounds of the invention, described below, are structurally different from compound A because of the novel substituents present on the aniline ring at the 2 position. Other differences between the compounds of the present invention and those disclosed in GB 2263110 are the substitutions on the aromatic ring at position 4 of the piperazine ring. These structural variations are neither disclosed nor suggested by GB 2263110, particularly with regard to compounds that can be used to improve urinary tract function. These structural variations result in compounds that are more potent than compound A in pharmacological tests predictive of activity on the lower urinary tract, in particular for activity against urinary incontinence.

Other compounds which have been found by the present inventors to be useful in the methods of the present invention, e.g., treatment of disorders of the urinary tract, are disclosed in US 4205173, EP 711757, DE 2405441, US 3472854, *Chem. Pharm. Bull.* 33:1826-1835 (1985), and *J. Med. Chem.* 7:721-725 (1964), all of which are incorporated by reference.

SUMMARY OF THE INVENTION

In one aspect, the invention relates to the use of compounds of the general formula I:



(I)

wherein

R represents a hydrogen atom or an alkylcarbonyl, a cycloalkylcarbonyl, substituted cycloalkylcarbonyl or monocyclic heteroarylcarbonyl group,

R_1 represents a hydrogen atom or a lower alkyl group,

R_2 represents a halogen atom or an alkoxy, phenoxy, nitro, cyano, acyl, amino, acylamino, alkylsulphonylamino, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, acylcarbamoyl, trifluoromethyl or polyfluoroalkoxy group, and

B represents a mono- or bicyclic aryl group, a substituted mono- or bicyclic aryl group, a mono- or bicyclic heteroaryl group, a substituted mono- or bicyclic heteroaryl group, a benzyl group or a substituted benzyl group,

for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract in a mammal.

In another aspect, the invention provides compounds of the general formula I (shown hereinbefore) wherein:

R represents a hydrogen atom or an alkylcarbonyl, a cycloalkylcarbonyl, substituted cycloalkylcarbonyl or monocyclic heteroarylcarbonyl group,

R_1 represents a hydrogen atom or a lower alkyl group,

R_2 represents a halogen atom or an alkoxy, phenoxy, nitro, cyano, acyl, amino, acylamino, alkylsulphonylamino, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, acylcarbamoyl, trifluoromethyl or polyfluoroalkoxy group, and

B represents a substituted monocyclic aryl group, a bicyclic aryl group, a substituted bicyclic aryl group, a mono- or bicyclic heteroaryl group, a substituted mono- or bicyclic heteroaryl group or a substituted benzyl group,

with the provisos that:

if both R and R_1 represent hydrogen atoms and R_2 represents a nitro group, then B does not represent a 2-methoxyphenyl, 4-chlorophenyl, 4-hydroxyphenyl, 3-acetylphenyl, 4-sulphamoylphenyl, 3,4,5-trimethoxyphenyl, 2-chloro-4-methylphenyl or 2-pyridyl group;

if both R and R_1 represent hydrogen atoms and R_2 represents a carbamoyl group, then B does not represent a 4-hydroxyphenyl group; and

if B represents an alkoxy substituted aryl group, then the alkoxy group must be at position 2 of the aryl ring;

The invention also includes the enantiomers, diastereomers, N-oxides, crystalline forms, hydrates and pharmaceutically acceptable salts of these compounds, as well as metabolites of these compounds having the same type of activity (hereafter sometimes referred to as "active metabolites").

The invention further provides pharmaceutical compositions comprising a compound of formula I or an enantiomer, diastereomer, N-oxide, crystalline form, hydrate or pharmaceutically acceptable salt of such a compound, in admixture with a pharmaceutically acceptable diluent or carrier.

As used herein with reference to variable R, alkylcarbonyl radicals include (C_1-C_6 alkyl)-carbonyl, cycloalkylcarbonyl includes cyclohexylcarbonyl, substituted cycloalkylcarbonyl includes cyclohexylcarbonyl substituted with alkyl or aryl groups and monocyclic heteroaryl radicals include monocyclic aromatic radicals of 5 to 7 ring atoms containing one or more hetero atoms (e.g., oxygen, nitrogen and sulphur). Monocyclic heteroarylcarbonyl has the same definition as monocyclic heteroaryl, but also comprises a carbonyl group linked to a carbon atom of the ring.

As used herein with reference to variable B, a mono or bicyclic aryl radical means an aromatic radical having 6 to 12 carbon atoms (e.g., phenyl or naphthyl). Preferred substituents for aryl radicals include lower alkyl, lower alkoxy (e.g., methoxy, ethoxy, propoxy, and butoxy), lower haloalkoxy (e.g., 2,2,2-trifluoroethoxy), halogen, amino, acylamino, alkylsulphonylamino, and (lower)alkylamino substituents.

As used with respect to variable B, monocyclic heteroaryl radical has the same meaning as for R above, and bicyclic heteroaryl radical means a bicyclic aromatic radical containing one or more heteroatoms (e.g., nitrogen, oxygen, sulphur) and 9 to 12 ring atoms.

Preferred substituents for the benzyl groups B are alkyl, alkoxy, halogen, nitro, cyano, amido, amino, alkylamino, acylamino, alkylsulphonylamino or acyl substituents.

Preferred substituents at B are optionally substituted monocyclic aryl and bicyclic heteroaryl. Most preferred substituents at B are alkoxyphenyl and mononitrogen-containing bicyclic heteroaryl.

R preferably represents a hydrogen atom or a cyclohexylcarbonyl, 1-methylcyclohexylcarbonyl, 1-phenylcyclohexylcarbonyl, 3-furylcarbonyl, 3-thienylcarbonyl, 4-pyridylcarbonyl, 3-pyridylcarbonyl or 2-pyrazinylcarbonyl group.

R_1 preferably represents a hydrogen atom or a methyl group.

R_2 preferably represents an iodine atom or a methoxy, phenoxy, nitro, cyano, acetyl, amino, acetamido, acetoxycarbonyl, carbamoyl, ethylcarbamoyl, dimethylcarbamoyl, cyclohexylcarbonylcarbamoyl, trifluoromethyl, trifluoromethoxy or 2-(2,2,2-trifluoro)-ethoxy group.

B preferably represents a 2-methoxyphenyl, 2,5-dichlorobenzyl or 4-indolyl group.

The compounds of the invention are useful treating neuromuscular dysfunctions of the lower urinary tract including without limitation dysuria, incontinence and enuresis. They may be used to ameliorate at least one of urinary urgency, increased urinary frequency, incontinence, urine leakage, enuresis, dysuria, urinary hesitancy, and difficulty in emptying bladder.

The compounds of the invention are useful for blocking 5-HT_{1A} serotonergic receptors, and, by virtue of this inhibitory activity, for the treatment of CNS disorders due to serotonergic dysfunction such as anxiety, depression, hypertension, sleep/wake cycle disorders, feeding behaviour, sexual function and cognition disorders in mammals, particularly in humans.

DETAILED DESCRIPTION OF THE INVENTION

All patents, patent applications, and literature references cited in the specification are hereby incorporated by reference in their entirety. In the case of inconsistencies, the present disclosure, including definitions, will prevail.

The present invention encompasses pharmaceutical formulations comprising the compounds disclosed above, as well as methods employing these formulations for treating neuromuscular dysfunction of the lower urinary tract such as dysuria, incontinence, enuresis, and the like. Dysuria includes urinary frequency, nocturia, urgency, and difficulty in emptying the bladder, i.e., a suboptimal volume of urine is expelled during micturition.

Incontinence syndromes include stress incontinence, urgency incontinence, and overflow incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

Without wishing to be bound by theory, it is believed that administration of the 5-HT_{1A} receptor antagonists of the invention prevents unwanted activity of the sacral reflex arc and/or cortical mechanisms that control micturition. Thus it is contemplated that a wide range of neuromuscular dysfunctions of the lower urinary tract can be treated using the compounds of the present invention.

An "effective amount" of the compound for treating a urinary disorder is an amount that results in measurable amelioration of at least one symptom or parameter of the disorders described above.

An effective amount for treating the disorder can easily be determined by empirical methods known to those of ordinary skill in the art, such as by establishing a matrix of dosages and frequencies of administration and comparing a group of experimental units or subjects to each point in the matrix. The exact amount to be administered to a patient will vary depending on the state and severity of the disorder and the physical condition of the patient. A measurable amelioration of any symptom or parameter can be determined by a physician skilled in the art or reported by the patient to the physician. It will be understood

that any clinically or statistically significant attenuation or amelioration of any symptom or parameter of urinary tract disorders is within the scope of the invention. Clinically significant attenuation or amelioration means perceptible to the patient and/or to the physician.

For example, a single patient may suffer from several symptoms of dysuria simultaneously, such as, for example, urgency and excessive frequency of urination, either or both of which may be reduced using the methods of the present invention. In the case of incontinence, any reduction in the frequency or volume of unwanted passage of urine is considered a beneficial effect of the present methods of treatment.

The compounds of the present invention may be formulated into liquid dosage forms with a physiologically acceptable carrier, such as, for example, phosphate buffered saline or deionized water. The pharmaceutical formulation may also contain excipients, including preservatives and stabilisers, that are well-known in the art. The compounds can be formulated into solid oral or non-oral dosage units such as, for example, tablets, capsules, powders, and suppositories, and may additionally include excipients, including without limitation lubricant(s), plasticizer(s), colorant(s), absorption enhancer(s), bactericide(s), and the like.

Modes of administration include oral and enteral, intravenous, intramuscular, subcutaneous, transdermal, transmucosal (including rectal and buccal), and by-inhalation routes. Preferably, an oral or transdermal route is used (i.e., via solid or liquid oral formulations, or skin patches, respectively).

The amount of the agent to be administered can range from between about 0.01 and about 25 mg/kg/day, preferably from between about 0.1 and about 10 mg/kg/day and most preferably from between about 0.2 and about 5 mg/kg/day. It will be understood that the single pharmaceutical formulations of the present invention need not contain the entire amount of the agent that is effective in treating the disorder, as such effective amounts can be reached by administration of a plurality of doses of such pharmaceutical formulations.

In a preferred embodiment of the present invention, compounds are formulated in capsules or tablets, each preferably containing 50-200 mg of the compounds of the invention, and are most preferably administered to a patient at a total daily dose of 50-400 mg, preferably 150-250 mg, and most preferably about 200 mg for relief of urinary incontinence and dysfunctions amenable to treatment with 5-HT_{1A} receptor ligands.

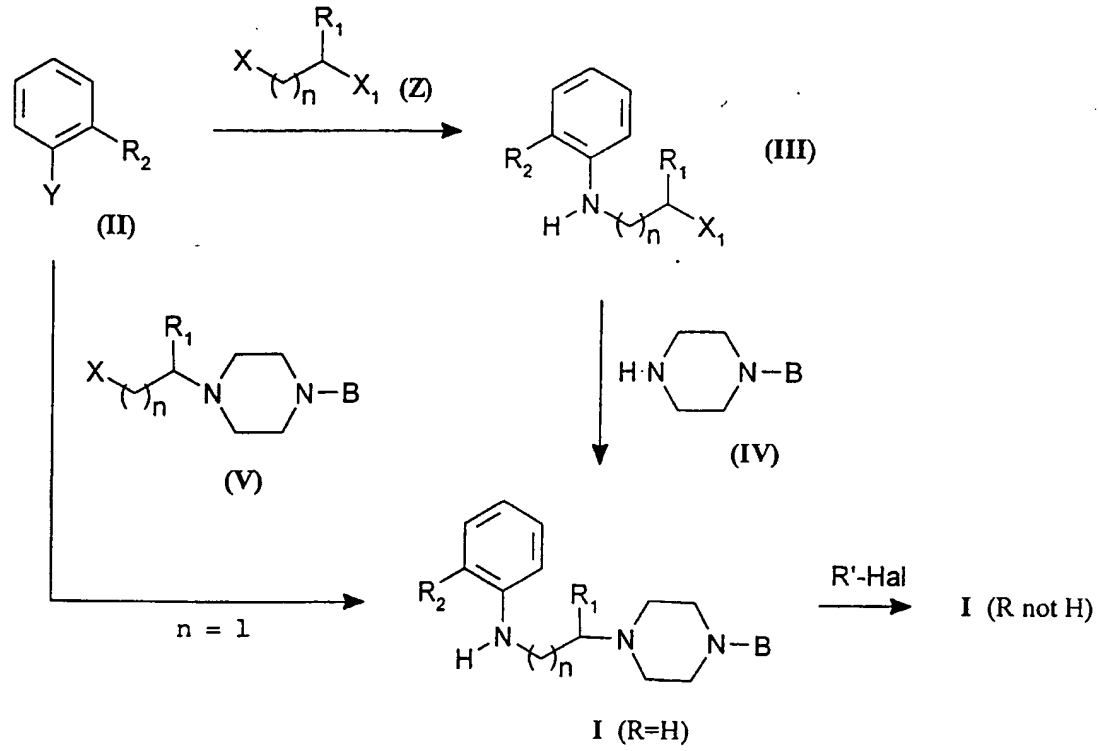
The methods, tables and examples provided below are intended to more fully describe preferred embodiments of the invention and to demonstrate its advantages and applicability, without in any way limiting the scope of the invention.

SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

The compounds of the invention may be prepared by the methods illustrated in the following reaction schemes, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures well known to those of ordinary skill in the art.

Unless otherwise specified, the substituents of the compounds and intermediates present in the reaction schemes are defined in the same manner as they are defined above in formula I. One method to synthesise compounds of formula **I** is depicted in Scheme I:

Scheme 1.



Ortho-substituted anilines of formula **II** (Y = NH_2) are alkylated with 1,ω-disubstituted alkanes (**Z**) to give product **III**. The reaction is carried out in an inert organic solvent, preferentially a polar aprotic solvent such as N,N-dimethylformamide (DMF), dimethylsulphoxide (DMSO), dioxane, tetrahydrofuran (THF), acetone, acetonitrile or chlorinated solvents such as dichloromethane, chloroform, 1,2-dichloroethane or a protic solvent such as n-butanol (n-BuOH). The reactions are generally performed at a temperature between 0 °C and +120 °C, in the presence of a proton acceptor such as triethylamine (Et_3N), diisopropylethylamine, or the like, and optionally in the presence of potassium iodide.

In compounds of formula **Z**, X and X_1 can be Cl, Br, I, aryl, or alkylsulphonyloxy groups.

Intermediates of formula **III** are used in the alkylation of suitable piperazine derivatives **IV** to give the compounds of formula **I** (where R=H).

These alkylations may be carried out in a chlorinated solvent such as dichloromethane, chloroform or 1,2-dichloroethane, or in a polar aprotic solvent such as DMF, THF, acetone, acetonitrile, or in a polar protic solvent such as *n*-BuOH, etc., or in an apolar solvent such as toluene, benzene, *n*-heptane, etc., at a temperature between 0 °C and 120 °C, optionally in the presence of a proton acceptor, such as Et_3N, 4-dimethylaminopyridine, potassium carbonate, caesium carbonate, and the like, and optionally in the presence of potassium iodide.

Piperazines of formula **IV** which are not commercially available may be prepared by reaction of the suitable B-NH_2 derivatives (which generally may be easily obtained by reduction of the corresponding B-NO_2 derivatives) with bis-(2-chloroethyl)amine or bis-(2-hydroxyethyl)amine in presence of excess hydrogen chloride. These reactions can be performed in aprotic solvents such as dimethylformamide, diglyme or toluene at a temperature between +40 °C and the reflux temperature of the solvent, generally in the presence of a base such as potassium carbonate, caesium carbonate, or the like, and optionally in the presence of potassium iodide.

Compounds of formula **V** can be conveniently prepared starting from compounds **V** in which X is a COO-lower alkyl group and n is n-1. Conventional reduction procedures (*e.g.*, use of lithium aluminium hydride or other metal complex hydrides) afford the corresponding compounds **V** in which X is CH_2OH and n is n-1, which can be in turn conventionally converted into compounds of formula **V** in which X is a leaving group as described above. The starting esters can be prepared by the nucleophilic displacement reaction of a monosubstituted piperazine on the appropriate 2-haloester.

Alternative procedures to obtain compounds of formula **V** consists in alkylating the appropriate monosubstituted piperazine derivatives with a compound with the formula X-$CH(R_1)(CH_2)_{n-1}CH_2$-OPrG or X-$(CH_2)_nCH(R_1)$-X where X is a leaving group and n has the same meaning as above, and PrG is a protecting group (e.g. O-tetrahydropyranyl), which can be removed after alkylation of the piperazine.

Another approach to synthesise intermediate compounds of formula **III** utilises starting materials with structure **II** (Y = halogen). These starting materials are reacted with compounds of formula **Z** in which X and X_1 are, respectively, NH_2 and OH. These alkylation reactions are carried out in an aprotic solvent such as DMF, toluene, or in a polar protic solvent such as *n*-BuOH, etc., at a temperature between +40 °C and +140 °C, in general using one equivalent or excess of a reagent of formula **Z** (X=NH_2) as a proton acceptor, as described by G. Doleschall et al., Tetrahedron, **32**, 57-64 (1976). The resulting aminoalcohols of formula **III** (X_1 = OH) are reacted with a chlorinating agent such as $POCl_3$, $SOCl_2$ or PCl_5 to give the intermediates, also of formula **III** (X_1 = Cl), or

with an alkyl or arylsulphonyl chloride to give the corresponding sulphonyl esters. These reactions are carried out in an aprotic solvent such as chloroform, DMF, pyridine, and the like at a temperature between +50 °C and the reflux temperature of the solvent.

Compounds of formula I (R=H) may also be obtained by alkylation of compounds of formula II (Y = NH_2) with intermediates of formula V, in which B, R_1 and n have the same meanings as above and X is a halogen atom such as chlorine or bromine, or a leaving group such as methanesulphonyloxy or p-toluenesulphonyloxy groups.

These reactions may be carried out without solvent or in an aprotic solvent such as dichloromethane, chloroform, DMF, THF, acetone, acetonitrile or in a protic solvent such as n-butanol, etc. at a temperature between 0 °C and +160 °C, optionally in the presence of a proton acceptor, such as Et_3N, potassium carbonate, caesium carbonate, 4-dimethylaminopyridine and the like, and optionally in the presence of potassium iodide.

Compounds of formula I where R_2 is CN can be also obtained from the compounds of formula I in which R_2 is $CONH_2$ by dehydration reactions. P_2O_5, PCl_5, Ph_3P, and the like may be used as dehydrating agents (J. March, Advanced Organic Chemistry, IV Ed., page 1041, Wiley Interscience, 1992). Dehydration reactions may be carried out in a chlorinated solvent such as dichloromethane, chloroform, carbon tetrachloride or in an aprotic solvent such as DMF, toluene, etc. at a temperature between +40 °C and the reflux temperature of the solvent, optionally in the presence of a base such as Et_3N.

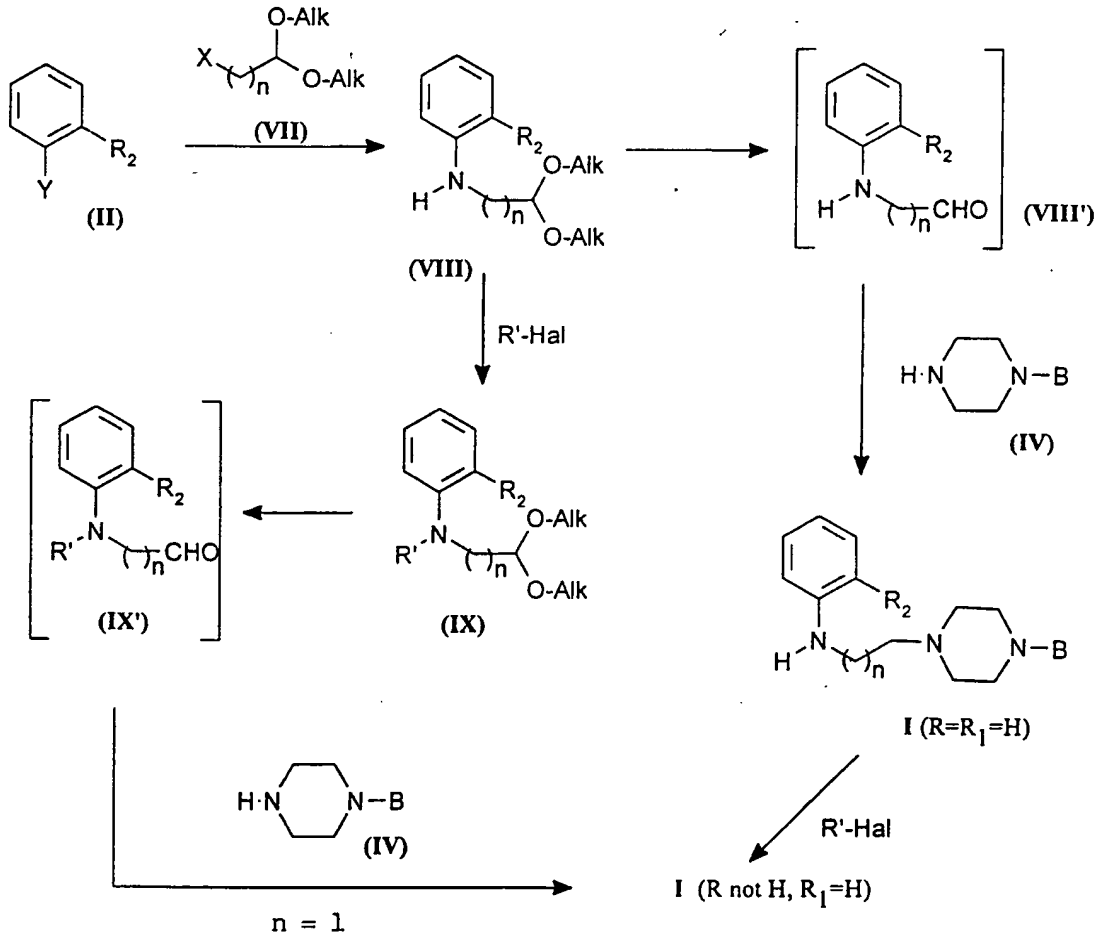
Alternatively, compounds of formula I (R=H) may be obtained by arylation of intermediates of formula V (X=NH_2) with a starting material of formula II (Y = Cl, Br, F, I or trifluoromethanesulphonyloxy). These reactions may be carried out using the same solvents and conditions as described above or by employing palladium complex catalysis (Synlett,p.329 (1996)).

Compounds of formula I in which R_2 is COalk can be synthesised from compounds I in which R_2 is H by an acylation reaction that can be carried out using boron trichloride as a Lewis acid and acetonitrile as a reagent in an aprotic solvent such as chloroform, 1,2-dichloroethane, toluene, etc. at temperatures between 0 °C and 100 °C, followed by acidic hydrolysis by treatment with HCl at 100 °C, (T. Sugasawa et al., Chem. Pharm. Bull., 33, 1826-1835 (1985)).

Compounds of formula I (R=H) are acylated to give compound I (R other than H) by reaction with an appropriate acyl halide R'Hal in which R' represents an alkylcarbonyl, cycloalkylcarbonyl or monocyclic heteroarylcarbonyl group and Hal represents a halogen atom. The reaction can be performed in aprotic solvents such as dichloromethane, chloroform, 1,2-dichloroethane, DMF, acetone, acetonitrile, toluene, etc., at temperatures between 0°C and 100°C, optionally in the presence of an organic base as a proton acceptor such as Et_3N, diisopropylethylamine (DIPEA), 4-dimethylaminopyridine, and the like.

Alternatively, compounds with formula I (i.e. where R_2=Br, I, OSO_2F or OSO_2CF_3) in which R is as defined above, but is not hydrogen, may be used to synthesise compounds of formula I in which R_2 is CN, $CONH_2$, $COCH_3$ or $COOCH_3$ by reaction of reagents such as trimethylsilyl isocyanate and t-butyl lithium (J. Org. Chem. 55, 3114 (1990)), lithium cyanide and tetrakis(triphenylphosphine)palladium(0) (EP 711757), carbon monoxide-methanol and palladium diacetate in the presence of 1,3-diphenylphosphinopropane (J. Org. Chem. 59, 6683 (1994)). Such reactions may be carried out in polar or apolar solvent such as THF, toluene, benzene, DMSO, and the like. Another method to synthesise compounds of formula I in which R_1 is H is depicted in Scheme 2, below.

Scheme 2.



Ortho-substituted halobenzenes of formula II (Y = halo) are used to arylate protected aminoalkylaldehydes of formula VII ($X=NH_2$) to give the corresponding protected arylaminoalkylaldehydes VIII. The reaction may be carried out in an aprotic solvent such as pyridine, DMF, toluene, or the like at a temperature between +40°C and 120°C,

optionally in the presence of a base such as Et_3N or employing palladium complex catalysts as above.

Another route for the preparation of intermediates of formula **VIII** consists in alkylating compounds of formula **II** ($Y=NH_2$) with protected reactive compounds of formula **VII** (X = halo) by conventional procedures known to those skilled in the art. Compounds with formula **VIII** are stable and are deprotected by standard methods just before their use in the following steps.

Aldehydes of formula **VIII'**, obtained from deprotection of compounds with formula **VIII**, may be reacted without isolation with N-substituted piperazines **IV** under reductive conditions to give compounds of formula **I** (R=R'=H). These reactions may be carried out in polar solvents such as methanol, ethanol or in chlorinated solvents, such as dichloromethane, chloroform, and the like, using alkali borohydrides such as $NaBH_4$ and $NaBH_3CN$, $NaBH(OAc)_3$ or using borane complexes such as BH_3-Py, optionally in the presence of acidic promoter, such as acetic acid, at temperatures between +10°C and 100°C.

Compounds of formula **I** (R=R'=H) may be acylated with R'Hal to give compounds of formula **I** where R is an alkylcarbonyl group by carrying out the reactions in the same conditions as described above for the final step of Scheme 1. Alternatively, intermediates of formula **VIII** may be acylated with R'Hal to give compounds of formula **IX** using the same conditions as described above.

Intermediates of formula **IX** are deprotected by well-known methods just before their use in the final step to give the corresponding aldehydes (**IX'**), which may be reacted with appropriate N-substituted piperazines of formula **IV** using alkali borohydrides such as $NaBH_4$, $NaBH_3CN$ or $NaBH(OAc)_3$, optionally in the presence of catalytic amounts of acetic acid, or of a titanium catalyst such as titanium tetraisopropoxide, yielding compounds of formula **I**. These reactions may be carried out in chlorinated solvents such as dichloromethane or chloroform, or in polar aprotic solvents such as methanol or ethanol at temperatures between +10°C and +100°C.

Example 1

1-[N-(2-nitrophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A mixture of 3.03 g of 2-chloro-1-nitrobenzene, 4.52 g of 1-(2-aminoethyl)-4-(2--methoxyphenyl)-piperazine, and 3.18 g of anhydrous potassium carbonate in 30 ml of *n*-butanol was stirred for 32 h at reflux. After cooling, the mixture was poured into water, then extracted with ethyl acetate and the organic phase dried on anhydrous sodium sulphate. The crude obtained by evaporating the solvent was purified by flash chromatography (ethyl acetate : petroleum ether 4:6) and the residue obtained after

evaporation of the solvents was taken up with diethyl ether, stirred and filtered giving 2.2 g (31%) of the title compound. M.p. 117-118 °C.

^{1}H-NMR ($CDCl_3$, δ): 8.50 (bs, 1H, NH), 8.19 (d,1H, aniline H3), 7.45 (dd, 1H, aniline H5), 7.08-6.78 (m, 5H, aniline H6 and methoxyphenyl ring CHs), 6.63 (dd, 1H, aniline H4), 3.86 (s, 3H, OCH_3), 3.40 (dt, 2H, $NHC\underline{H}_2CH_2$), 3.27-3.04 (m, 4H, piperazine protons), 2.80-2.62 (m, 6H, $NHCH_2C\underline{H}_2$ and piperazine protons).

Example 2

1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

Cyclohexylcarbonyl chloride (0.98 ml) and triethylamine (1.03 ml) were added in sequence to a solution containing 2.1 g of the compound prepared in Example 1 and 15 ml of 1,2-dichloroethane. The mixture was stirred for 16 h at reflux. Finally it was cooled, diluted with chloroform, washed with 1N sodium hydroxide and water. The organic phase was dried on anhydrous sodium sulphate and the crude obtained after evaporation of the solvents was purified via flash chromatography (ethyl acetate : petroleum ether 1:1) and subsequently crystallised from cyclohexane giving 1.79 g (65%) of the title compound.

Melting point : 119-121 °C.

^{1}H-NMR ($CDCl_3$, δ): 8.04 (d, 1H, nitrophenyl ring H3), 7.65-7.47 (m, 3H, nitrophenyl ring H4,5,6), 7.10-6.75 (m, 4H, methoxyphenyl ring CHs), 4.15-3.92 (m, 1H, $C(O)NCH(\underline{H})CH_2$), 3.83 (s, 3H, OCH_3), 3.70-3.50 (m, 1H, $C(O)NC\underline{H}(H)CH_2$), 3.10-2.80 (m, 4H, piperazine protons), 2.80-2.40 (m, 6H, piperazine protons and $C(O)NCH_2C\underline{H}_2$), 2.10-0.75 (m, 11H, cyclohexyl protons).

By conventional methods, the following salts of the compound of Example 2 were prepared :

monohydrochloride, m.p. 183-187°C (acetone : diethyl ether) ;
monomethanesulphonate, m.p. 150-153°C (acetone) ;
monomethanesulphonate hydrate, m.p. 136-140°C.

Example 3

1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A solution of 2.09 g of 2-trifluoromethoxyaniline and 3.15 g of 1-(2-chloroethyl)-4-(2-methoxyphenyl)-piperazine in 20 ml of *n*-butanol was stirred at 100°C for 2 hours. The mixture was then cooled, diluted with water, alkalinised with 2N sodium hydroxide and extracted with chloroform. The organic phase was dried on anhydrous sodium sulphate, evaporated until dry and the crude purified via flash chromatography (ethyl acetate : petroleum ether 3:7) and subsequently crystallised from ethanol giving 0.55 g (12%) of the title compound. Melting point: 69.5-71°C.

^{1}H-NMR ($CDCl_3$, δ): 8.02-7.85 (br, 1H, NH), 7.43-7.27 (m, 2H, aniline CHs), 7.03-6.80 (m, 4H, methoxyphenyl ring CHs), 6.72 (dd, 1H, aniline CH), 6.57 (t, 1H, aniline CH), 3.86 (s, 3H, OCH_3), 3.43-3.23 (m, 2H, $NHCH_2CH_2$), 3.23-3.03 (m, 4H, piperazine protons), 2.85-2.60 (m, 6H, piperazine protons and $NHCH_2CH_2$).

Example 4

1-[N-(2-trifluoromethoxyphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 2, except that 1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 3, was used in place of 1-[N-(2-nitrophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine and that 4-dimethylaminopyridine was used in place of triethylamine, the mixture being heated for 1.5 h at reflux. The crude material was purified via flash chromatography (ethyl acetate : petroleum ether 4:6). Yield: 44%.

^{1}H-NMR ($CDCl_3$, δ): 7.48-7.25 (m, 4H, trifluoromethoxyaniline ring CHs), 7.02-6.81 (m, 4H, methoxyphenyl ring CHs), 4.40-4.20 (m, 1H, $C(O)NCH(H)CH_2$), 3.84 (s, 3H, OCH_3), 3.36-3.18 (m, 1H, $C(O)NCH(H)CH_2$), 3.10-2.90 (m, 4H, piperazine protons), 2.75-2.45 (m, 6H, piperazine protons and $C(O)NCH_2CH_2$), and 2.03-1.80 (m, 1H, CHC(O)), 1.75-0.80 (m, 10H, cyclohexyl protons).

Example 5

1-[N-(2-phenoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine . 3HCl

Operating as described in Example 3, but using 2-phenoxyaniline in place of 2-trifluoromethoxyaniline, crude 1-[N-(2-phenoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine was obtained. This was purified via flash chromatography (ethyl acetate). The residue was dissolved in ethanol, the solution was acidified by using 2N ethanolic hydrogen chloride and subsequently diethyl ether was added giving 45% of the title compound after filtration.

Melting point: 184-187 °C.

^{1}H-NMR (DMSO-d_6, δ): 8.70-7.60 (m, 4H, 3^+NH and NH), 7.32 (t, 2H, aromatics), 7.10-6.85 (m, 9H, aromatics), 6.80 (dd, 1H, aromatic), 6.63 (t, 1H, aromatic), 3.78 (s, 3H, OCH_3), 3.65-3.00 (m, 12H, piperazine protons and $NHCH_2CH_2$).

Example 6

1-[N-(2-phenoxyphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 4, except that 1-[N-(2-phenoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as

described in Example 5, was used in place of 1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, the mixture being heated for 2.5 h at reflux. The crude was purified via flash chromatography (ethyl acetate : petroleum ether 7:3). Yield: 32%.

^{1}H-NMR ($CDCl_3$, δ): 7.40-7.20 (m, 4H, aromatics), 7.10 (t, 2H, aromatics), 7.05-6.80 (m, 7H, aromatics), 4.21-4.03 (m, 1H, C(O)NC(H)$\underline{H}CH_2$), 3.83 (s, 3H, OCH_3), 3.55-3.40 (m, 1H, C(O)NC($\underline{H}$)HCH_2), 3.10-2.93 (m, 4H, piperazine protons), 2.75-2.50 (m, 6H, piperazine protons and C(O)$NCH_2C\underline{H_2}$), and 2.25-2.05 (m, 1H, CHC(O)), 1.80-0.80 (m, 10H, cyclohexyl protons).

Example 7

1-[N-(2-iodophenyl)-2-aminoethyl]-4-(2-methoxyphenyl) piperazine

The title compound was prepared following the procedure described in Example 3, except that 2-iodoaniline was used in place of 2-trifluoromethoxyaniline and that heating was at 90°C for 7 h. The crude was purified via flash chromatography (ethyl acetate : petroleum ether 1:4). Yield: 37%.

^{1}H-NMR ($CDCl_3$, δ): 7.65 (dd, 1H, aniline H3). 7.20 (dd. 1H. aniline H5), 7.07-6.80 (m, 4H, methoxyphenyl ring CHs), 6.55 (dd,1H, aniline H4). 6.45 (dd, 1H, aniline H6), 5.15-5.03 (br, 1H, NH), 3.87 (s, 3H, OCH_3), 3.30-3.05 (m. 6H, piperazine protons and $NHC\underline{H_2}CH_2$), 2.83-2.65 (m, 6H, piperazine protons and $NHCH_2C\underline{H_2}$).

Example 8

1-[N-(2-iodophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 4, except that 1-[N-(2-iodophenyl)-2-aminoethyl]-4-(2-methoxyphenyl) piperazine, prepared as described in Example 7, was used in place of 1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, the mixture being heated for 7 h at reflux. Yield: 73%.

^{1}H-NMR ($CDCl_3$, δ): 8.95 (dd, 1H, iodophenyl ring H3), 7.45-7.35 (m, 2H, iodophenyl ring CHs), 7.15-6.80 (m, 5H, methoxyphenyl ring CHs and remaining iodophenyl ring CH), 4.53-4.37 (m, 1H, C(O)NC(H)$\underline{H}CH_2$), 3.84 (s, 3H, OCH_3), 3.20-2.95 (m, 5H, C(O)NC($\underline{H}$)HCH_2 and piperazine protons), 2.77-2.50 (m, 7H, C(O)$NCH_2C\underline{H_2}$, piperazine protons and CHC(O)), 1.90-0.80 (m, 10H, cyclohexyl protons).

Example 9

1-[N-(2-carbamoylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 3, except that 2-aminobenzamide was used in place of 2-trifluoromethoxyaniline. The crude was purified via flash chromatography (ethyl acetate) and subsequently crystallised from ethanol.

Yield: 36%. Melting point: 134-136° C

^{1}H-NMR ($CDCl_3$, δ): 8.02-7.85 (br, 1H, NH), 7.41-7.26 (m, 2H, aniline H3,5), 7.05-6.78 (m, 4H, methoxyphenyl ring CHs), 6.73 (dd,1H, aniline H6), 6.58 (t, 1H, aniline H4), 5.80-5.45 (br, 2H, $CONH_2$), 3.86 (s, 3H, OCH_3), 3.33 (t, 2H, $NHCH_2CH_2$), 3.20-3.02 (m, 4H, piperazine protons), 2.83-2.62 (m, 6H, $NHCH_2CH_2$, and piperazine protons).

Example 10

1-[N-(2-cyanophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A mixture containing 0.2 g of 1-[N-(2-aminocarbonylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 9, 0.26 g of triphenylphosphine, 0.08 ml of triethylamine, 0.5 ml of carbon tetrachloride and 10 ml of 1,2-dichloroethane was stirred for 3 h at reflux. The residue obtained after evaporation of the solvent was purified via flash chromatography (dichloromethane : methanol 98:2) giving 0.14 g (74%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 7.40-7.30 (m, 2H, aniline H4,6), 7.05-6.80 (m, 4H, methoxyphenyl ring CHs), 6.70-6.57 (m, 2H, aniline H3,5), 5.45-5.30 (br, 1H, NH), 3.86 (s, 3H, OCH_3), 3.25 (q, 2H, $NHCH_2CH_2$), 3.20-3.00 (m, 4H, piperazine protons), 2.85-2.60 (m, 6H, $NHCH_2CH_2$ and piperazine protons).

Example 11

1-[N-(2-acetylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl) piperazine

The procedure described in Example 3 was followed, except that aniline was used in place of 2-trifluoromethoxyaniline and no solvent was used. The crude was purified via flash chromatography (petroleum ether : ethyl acetate 8:2) to give 1-(N-phenyl-2-aminoethyl)-4-(2-methoxyphenyl)-piperazine. Yield: 77%

^{1}H-NMR ($CDCl_3$, δ): 7.30-7.10 (m, 2H, aniline H2,6), 7.10-6.80 (m, 4H, methoxyphenyl ring CHs), 6.80-6.58 (m, 3H, aniline H3,4,5), 4.35 (bs, 1H, NH), 3.87 (s, 3H, OCH_3), 3.30-3.15 (m, 2H, $NHCH_2CH_2$), 3.15-2.98 (m, 4H, piperazine protons), 2.80-2.60 (m, 6H, piperazine protons and $NHCH_2CH_2$).

A solution of 1M boron tribromide in dichloromethane (2.37 ml) was dropped into another solution containing 0.74 g of 1-(N-phenyl-2-aminoethyl)-4-(2-methoxyphenyl)-piperazine, prepared as above described, in 10 ml of dichloromethane stirred at -3°C in nitrogen atmosphere. Subsequently, 0.25 ml of acetonitrile at room temperature was added and the mixture was stirred for 1 h at room temperature and for 8 h until precipitation. After

cooling at room temperature, the mixture was treated with a 10% aqueous solution of sodium carbonate and the organic phase which separated was dried on anhydrous sodium sulphate and evaporated to dryness. The crude was purified via flash chromatography (dichloromethane : methanol 98:2) and the residue crystallised from ethanol giving 0.33 g (39%) of the title compound. Melting point: 92-94°C.

^{1}H-NMR ($CDCl_3$, δ): 9.12-8.95 (br, 1H, NH), 7.75 (dd, 1H, aniline H3), 7.35 (dt, 1H, aniline H5), 7.05-6.80 (m, 4H, methoxyphenyl ring CHs), 6.73 (dd, 1H, aniline H4), 6.58 (dt, 1H, aniline H6), 3.86 (s, 3H, OCH_3), 3.35 (q, 2H, $NHC\underline{H}_2CH_2$), 3.20-3.02 (m, 4H, piperazine protons), 2.85-2.61 (m, 6H, $NHCH_2C\underline{H}_2$ and piperazine protons), 2.58 (s, 3H, $COCH_3$).

Example 12

1-[N-(2-nitrophenyl)-2-aminoethyl]-4-(4-indolyl)-piperazine

A mixture containing 0.49 g of N-(2-chloroethyl)-2-nitroaniline, prepared according to the procedure described by Ramage G.R. et al. in *J. Chem. Soc.* 4406-4409 (1952), 0.55 g of 1-(4-indolyl)-piperazine (prepared according to WO 95/33743), 1 ml of triethylamine and 3 ml of dimethylformamide was heated at reflux while stirring under nitrogen for 2.5 h. After cooling at room temperature, the mixture was poured into water and extracted with dichloromethane. The organic phase was dried on anhydrous sodium sulphate and evaporated to dryness. The residue was purified via flash chromatography (ethyl acetate : petroleum ether 3:7) giving 0.35 g (40%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 8.60-8.45 (br, 1H, aniline NH), 8.18 (dd, 1H, aniline H3), 8.20-8.10 (br, 1H, indole NH), 7.43 (td, 1H, aniline H5), 7.20-7.05 (m, 3H, indole H3,6,7), 6.85 (dd, 1H, aniline H4), 6.70-6.57 (m, 2H, aniline H6 and indole H5), 6.50 (t, 1H, indolylic H2), 3.45 (q, 2H, $NHC\underline{H}_2CH_2$), 3.35-3.25 (m, 4H, piperazine protons), 3.85-2.70 (m, 6H, $NHCH_2C\underline{H}_2$ and piperazine protons).

Example 13

1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(4-indolyl)-piperazine

The title compound was prepared following the procedure described in Example 4, except that 1-[N-(2-nitrophenyl)-2-aminoethyl]-4-(4-indolyl)-piperazine, prepared as described in Example 12, was used in place of 1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, the mixture being heated for 5 h at reflux. The crude was purified via flash chromatography (ethyl acetate : petroleum ether 7:3, then only ethyl acetate was used and at the end only dichloromethane). Yield: 32%

^{1}H-NMR ($CDCl_3$, δ): 8.37-8.20 (br, 1H, NH), 8.05 (dd, 1H, nitrophenyl ring H3), 7.65-7.45 (m, 3H, nitrophenyl ring H4,5,6), 7.20-7.00 (m, 3H, indole H3,6,7), 6.55 (dd, 1H, indole H5), 6.50 (t, 1H, indole H2), 4.15-3.95 (m, 1H, $C(O)NC(\underline{H})HCH_2$), 3.70-3.55 (m,

1H, C(O)NC(H)HCH$_2$), 3.25-2.95 (m, 4H, piperazine protons), 2.75-2.45 (m, 7H, C(O)NCH$_2$CH$_2$, CHC(O), piperazine protons), 2.10-0.80 (m, 10H, cyclohexyl protons).

Example 14

1-[N-(2-nitrophenyl)-2-aminoethyl)-4-(2,5-dichlorobenzyl)-piperazine

2,5-Dichlorobenzyl chloride (2.01 g) was added to a mixture of 1.94 g of 1-ethoxycarbonyl-piperazine and 3.45 g of anhydrous potassium carbonate in 20 ml of dimethylformamide stirred at room temperature under a nitrogen atmosphere. After 24 h of stirring at the same temperature, the reaction mixture was poured into water and extracted with ethyl acetate. The organic phase, which was dried on anhydrous sodium sulphate, was evaporated to dryness under vacuum. The oily residue was purified via flash chromatography (petroleum ether : ethyl acetate 85:15) giving 2 g (63%) of 1-(2,5-dichlorobenzyl)-4-ethoxycarbonyl-piperazine.

^{1}H-NMR ($CDCl_3$, δ): 7.50 (d, 1H, aromatic H6), 7.27 (d, 1H, aromatic H3), 7.15 (dd, 1H, aromatic H4), 4.13 (q, 2H, CH_3CH_2O), 3.58 (s, 2H, benzyl CH_2), 3.55-3.45 (m, 4H, piperazine protons), 2.50-2.42 (m, 4H, piperazine protons), 1.26 (t, 3H, CH_3CH_2O).

A solution containing 13 g of 1-(2,5-dichlorobenzyl)-4-ethoxycarbonyl-piperazine, prepared as above described, in 35 ml of 37% hydrochloric acid was stirred for 40 h at reflux. Subsequently, 30 ml of water and 30 ml of ethyl acetate were added at room temperature, adjusting the pH to 11 via addition of 35% sodium hydroxide. The organic phase was dried on anhydrous sodium sulphate and evaporated to dryness under vacuum. The crude was purified via flash chromatography (chloroform : methanol 7:3) giving 4.46 g (50%) of 1-(2,5-dichlorobenzyl)-piperazine .

^{1}H-NMR ($CDCl_3$, δ): 7.50 (d, 1H, aromatic H6), 7.26 (d, 1H, aromatic H3), 7.14 (dd, 1H, aromatic H4), 3.55 (s, 2H, benzyl CH_2), 3.00-2.85 (m, 4H, piperazine protons), 2.55-2.48 (m, 4H, piperazine protons), 1.76 (s, 1H, NH).

The title compound was prepared and purified following the method described in Example 12, but using 1-(2,5-dichlorobenzyl)-piperazine, prepared as above described, in place of 1-(4-indolyl)-piperazine and using 4-dimethylaminopyridine in place of triethylamine and carrying out the reaction at 120°C for 8 h. Yield: 35%.

^{1}H-NMR ($CDCl_3$, δ): 8.45 (bs, 1H, NH), 8.10 (d, 1H, aniline H3), 7.45 (d, 1H, dichlorophenyl ring H6), 7.38 (dd, 1H, aniline H5), 7.25 (d, 1H, dichlorophenyl ring H3), 7.10 (dd, 1H, dichlorophenyl ring H4), 6.77 (d, 1H, aniline H6), 6.55 (dd, 1H, aniline H4), 3.59 (s, 2H, benzyl CH_2), 3.35 (dt, 2H, NHCH_2CH$_2$), 2.73 (t, 2H, NHCH$_2$CH_2), 2.70-2.38 (m, 8H, piperazine protons).

Example 15

1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2,5-dichlorobenzyl)-piperazine

The title compound was prepared following the procedure described in Example 2, except that 1-[N-(2-nitrophenyl)-2-aminoethyl)-4-(2,5-dichlorobenzyl)-piperazine, prepared as described in Example 14, was used in place of 1-[N-(2-nitrophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, and heating was 12 h at reflux. The crude was purified via flash chromatography (ethyl acetate : petroleum ether 4:6). Yield: 22%.

^{1}H-NMR ($CDCl_3$, δ): 8.03 (dd, 1H, nitrophenyl ring H3), 7.75-7.40 (m, 4H, dichlorophenyl ring H6 and nitrophenyl ring H4,5,6), 7.25 (d, 1H, dichlorophenyl ring H3), 7.10 (dd, 1H, dichlorophenyl ring H4), 4.05-3.90 (m, 1H, C(O)NC(H)$\underline{H}CH_2$), 3.65-3.50 (m, 1H, C(O)NC($\underline{H}$)HCH_2, 3.52 (s, 2H, benzyl CH_2), 2.70-2.20 (m, 10H, C(O)N$CH_2C\underline{H}_2$, piperazine protons), 2.00-0.70 (m, 11H, cyclohexyl protons).

Example 16

1-[N-(2-cyclohexylcarbamoylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 4, except that 1-[N-(2-carbamoylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 9, was used in place of 1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, the mixture being heated for 6 h at reflux in the presence of 2 molar equivalents of cyclohexylcarbonyl chloride. The crude was purified via flash chromatography (dichloromethane : methanol 95:5). Yield: 55%.

^{1}H-NMR (DMSO-d_6, δ): 12.10-11.80 (br, 1H, NH), 8.08 (dd,1H, phenylcarbonyl H3), 7.88-7.68 (m, 2H, phenylcarbonyl H5,6), 7.47 (dt, 1H, phenylcarbonyl H4), 7.00-6.80 (m, 4H, methoxyphenyl ring CHs), 4.50-4.33 (m, 2H, C(O)N$\underline{H}_2CH_2$), 3.75 (s, 3H, OCH_3), 3.15-2.85 (m, 5H, CHC(O) and piperazine protons), 2.80-2.68 (m, 2H, C(O)N$CH_2C\underline{H}_2$), 2.68-2.54 (m, 4H, piperazine protons), 2.28-2.08 (m, 1H, CHC(O)), 1.97-1.05 (m, 20H, cyclohexyl protons).

Example 17

1-[N-(2-methoxycarbonylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A mixture of 0.93 g of methyl anthranilate, 2 g of 1-(2-chloroethyl)-4-(2-methoxyphenyl)-piperazine, 0.88 g of sodium acetate and 5 ml of water was stirred for 24 h at reflux. After cooling to room temperature, the mixture was extracted with ethyl acetate. The organic phase was dried on anhydrous sodium sulphate and evaporated to dryness. The residue was purified by flash chromatography (dichloromethane : methanol 98:2) giving 0.41 g (18%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 7.90 (dd, 1H, aniline H3), 7.90-7.70 (br, 1H, NH), 7.35 (td,1H, aniline H5), 7.06-6.80 (m, 4H, methoxyphenyl ring CHs), 6.70 (dd, 1H, aniline H6), 6.58 (td, 1H, aniline H4), 3.87 and 3.85 (2s, 6H, $COOCH_3$ and OCH_3), 3.43-3.30 (m, 2H, $NHCH_2CH_2$), 3.22-3.05 (m, 4H, piperazine protons), 2.83-2.67 (m, 6H, $NHCH_2CH_2$ and piperazine protons).

Example 18

1-[N-(2-methoxycarbonylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 4, except that 1-[N-(2-methoxycarbonylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 17, was used in place of 1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, the mixture being heated for 9 h at reflux. The crude was purified by flash chromatography (dichloromethane : methanol 95:5). Yield: 38%

^{1}H-NMR ($CDCl_3$, δ): 8.03 (dd, 1H, methoxycarbonylphenyl ring H3), 7.57 (dt, 1H, methoxycarbonylphenyl ring H4), 7.45 (dt, 1H, methoxycarbonylphenyl ring H5), 7.37 (dd, 1H, methoxycarbonylphenyl ring H6), 7.03-6.80 (m, 4H, methoxyphenyl ring CHs), 4.38-4.15 (m, 1H, $C(O)NC(H)HCH_2$), 3.86 and 3.83 (2s, 6H, $COOCH_3$ and OCH_3), 3.33-3.15 (m, 1H $C(O)NC(H)HCH_2$), 3.10-2.93 (m, 4H, piperazine protons), 2.75-2.50 (m, 4H, piperazine protons), 2.56 (t, 2H, $C(O)NCH_2CH_2$), 2.00-1.83 (m, 1H, CHC(O)), 1.80-0.80 (m, 10H, cyclohexyl protons).

Example 19

1-[N-(2-dimethylcarbamoyl-phenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 3, except that N,N-dimethyl-2-aminobenzamide was used in place of 2-trifluoromethoxyaniline. The crude was purified via flash chromatography (ethyl acetate : methanol 97:3). Yield: 19%.

^{1}H-NMR ($CDCl_3$, δ): 7.25 (dt, 1H, aniline H5), 7.09 (dd, 1H, aniline H3), 7.06-6.80 (m, 4H, methoxyphenyl ring CHs), 6.68 (dd, 1H, aniline H6), 6.66 (dt, 1H, aniline H4), 5.50-5.10 (br, 1H, NH), 3.86 (s, 3H, OCH_3), 3.23 (t, 2H, $NHCH_2CH_2$), 3.18-3.08 (m, 4H, piperazine protons), 3.05 (s, 6H, $N(CH_3)_2$), 2.78-2.62 (m, 6H, $NHCH_2CH_2$ and piperazine protons).

Example 20

1-[N-(2-methoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared and purified following the procedure described in Example 3, except that 2-methoxyaniline was used in place of 2-trifluoromethoxyaniline, and heating was at 100°C for 4 h. Yield: 50%

^{1}H-NMR ($CDCl_3$, δ): 7.05-6.85 (m, 5H, methoxyphenyl ring CHs and aniline CH), 6.85-6.60 (m, 3H, aniline CHs), 3.87 and 3.85 (2s, 6H, 2 OCH_3), 3.25 (t, 2H, $NHCH_2CH_2$), 3.18-3.05 (m, 4H, piperazine protons), 2.80-2.65 (m, 6H, $NHCH_2CH_2$ and piperazine protons).

Example 21

1-[N-(2-dimethylcarbamoyl-phenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 4, except that 1-[N-(2-dimethylcarbamoyl-phenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 19, was used in place of 1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, the mixture being heated for 5 h at reflux. The crude was purified by flash chromatography (dichloromethane : methanol 93:7). Yield : 36%.

^{1}H-NMR ($CDCl_3$, δ) : 7.50-7.30 (m, 4H, benzamide ring CHs), 7.06-6.80 (m, 4H, methoxyphenyl ring CHs), 4.85 (s, 3H, OCH_3), 4.60-4.40 (m, 1H, $CONCH(H)CH_2N$), 3.67-3.40 (m, 1H, $CONCH(H)CH_2N$), 3.35-2.95 (m, 4H, piperazine protons), 3.10 and 2.90 (2s, 6H, $N(CH_3)_2$), 2.85-2.45 (m, 6H, piperazine protons and $CONCH_2CH_2N$), 2.10-1.90 (m, 1H, CHC(O)), 1.90-0.80 (m, 10H, cyclohexyl protons).

Example 22

1-[N-(2-trifluoromethylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 3, except that 2-trifluoromethylaniline was used in place of 2-trifluoromethoxyaniline. The crude was purified via flash chromatography (ethyl acetate : petroleum ether 2:8). Yield: 14%.

^{1}H-NMR ($CDCl_3$, δ): 7.50-7.30 (m, 4H, aniline CHs), 7.10-6.80 (m, 4H, methoxyphenyl ring CHs), 5.50-5.38 (br, 1H, NH), 3.86 (s, 3H, OCH_3), 3.30-3.18 (m, 2H, $NHCH_2CH_2$), 3.18-3.05 (m, 4H, piperazine protons), 2.75 (t, 2H, $NHCH_2CH_2$), 2.80-2.63 (m, 4H, piperazine protons).

Example 23

1-[N-(2-methoxyphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 2, except that 1-[N-(2-methoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine. prepared as

described in Example 20, was used in place of 1-[N-(2-nitrophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine and that the mixture was refluxed for 6 h. The crude was purified by flash chromatography (CH_2Cl_2-MeOH 9.5:0.5). Yield: 59%.

^{1}H-NMR ($CDCl_3$, δ): 7.38 (dd, 1H, methoxyphenylaniline H6), 7.26 (dd, 1H, methoxyphenylaniline H4), 7.10-6.85 (m, 6H, methoxyphenylaniline H3, H5 and methoxyphenyl protons), 4.35-4.12 (m, 1H, CONC<u>H</u>(H)CH_2), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.55-3.33 (m, 1H, CONCH(<u>H</u>)CH_2), 3.20-2.98 (m, 4H, piperazine protons), 2.80-2.50 (m, 6H, piperazine protons and $CONCH_2C\underline{H}_2$), 2.05 (tt, 1H, CHC(O)), 1.30-0.85 (m, 10H, cyclohexyl protons).

Example 24

1-[N-(2-ethylcarbamoyl-phenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 3, except that 2-ethylcarbamoyl-aniline was used in place of 2-trifluoromethoxyaniline and the mixture was refluxed for 5 h. The crude was purified by flash chromatography (dichloromethane : methanol 9.7:0.3). Yield: 12%.

^{1}H-NMR ($CDCl_3$, δ): 7.50 (t, 1H, CON<u>H</u>Et), 7.38-7.23 (m, 2H, aniline H4, H6), 7.07-6.83 (m, 4H, methoxyphenyl ring CHs), 6.70 (dd, 1H, aniline H3), 6.60 (dd, 1H, aniline H5), 6.13-5.90 (br, 1H, N<u>H</u>CH_2CH_2), 3.86 (s, 3H, OCH_3), 3.53-3.40 (m, 2H, $CONHC\underline{H}_2CH_3$), 3.33 (q, 2H, $NHC\underline{H}_2CH_2$), 3.18-3.02 (m, 4H, piperazine protons), 2.83-2.63 (m, 6H, piperazine protons and $NHCH_2C\underline{H}_2$), 1.23 (t, 3H, $CONHCH_2C\underline{H}_3$).

Example 25

1-[N-(2-ethylcarbamoyl-phenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 2, except that 1-[N-(2-ethylcarbamoyl-phenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 24, was used in place of 1-[N-(2-nitrophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine and that the mixture was refluxed for 12 h using toluene as solvent instead of 1,2-dichloroethane. The crude was purified by flash chromatography (dichloromethane : methanol 9.5:0.5). Yield: 43%.

^{1}H-NMR ($CDCl_3$, δ): 9.30-9.12 (br, 1H, CON<u>H</u>Et), 7.80 (dd, 1H, aniline H6), 7.45 (dd, 1H, aniline H4), 7.35 (dd, 1H, aniline H5), 7.20 (dd, 1H, aniline H3), 7.05-6.75 (m, 4H, methoxyphenyl ring CHs), 4.47 (dt, 1H, CONCH(<u>H</u>)CH_2N), 3.82 (s, 3H, OCH_3), 3.73-3.50 (m, 1H, CONHCH(<u>H</u>)CH_3), 3.32-3.10 (m, 1H, $CONHC\underline{H}(H)CH_3$), 3.03-2.25 (m, 5H, CONC<u>H</u>(H)CH_2N and piperazine protons), 2.65-2.16 (m, 7H, $CONCH_2C\underline{H}_2$, piperazine protons and CHC(O)), 1.70-0.80 (m, 10H, cyclohexyl protons), 1.18 (t, 3H, $CONHCH_2C\underline{H}_3$).

Example 26

1-[N-(2-trifluoromethylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A solution of 2-trifluoromethylaniline (3 ml), triethylamine (3.5 ml) and dichloromethane (30 ml) was stirred at room temperature under nitrogen. 3.34 ml of cyclohexylcarbonyl chloride was added dropwise. After stirring for 2½ hours at room temperature, the mixture was poured into water and alkalinised with 1N sodium hydroxide. The organic phase was dried on anhydrous sodium sulphate and the crude was crystallised from ethanol to give 3.82 g (59%) of 1-cyclohexylcarbamoyl-2-trifluoromethyl-benzene. M.p. 153-154°C.

^{1}H-NMR ($CDCl_3$, δ): 8.20 (dd, 1H, trifluoromethylphenyl ring CH), 7.60-7.40 (m, 3H, trifluoromethylphenyl ring CHs and NH), 7.12 (ddd, 1H, trifluoromethylphenyl ring CH), 2.30 (tt, 1H, CHC(O)), 2.10-1.20 (m, 10H, cyclohexyl protons).

A mixture of 0.2 g of 1-cyclohexylcarbamoyl-2-trifluoromethyl-benzene, prepared as above described, 0.37 g of 1-(2-chloroethyl)-4-(2-methoxyphenyl)-piperazine, 0.5 ml of 50% (w/w) sodium hydroxide, 0.16 g of TEBAC and 2 ml of toluene was stirred at 80°C for 3.5 h. An additional 0.2 g of 1-cyclohexylcarbamoyl-2-trifluoromethyl-benzene was then added and after 6 h stirring at 80°C the mixture was poured into water and extracted with dichloromethane. The organic phase was dried on anhydrous sodium sulphate and evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate : petroleum ether 3:7) to give 0.12 g (17%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 7.77 (dd, 1H, trifluoromethylphenyl ring CH), 7.70-7.45 (m, 3H, trifluoromethylphenyl ring CHs), 7.10-6.80 (m, 4H, methoxyphenyl ring CHs), 4.70-4.50 (m, 1H, CONC<u>H</u>(H)CH_2N), 3.85 (s, 3H, OCH_3). 3.20-2.90 (m, 5H, CONCH(<u>H</u>)CH_2N and piperazine protons), 2.85-2.45 (m, 7H, CHC(O), $CONCH_2C\underline{H}_2$N and piperazine protons), 1.90-0.75 (m, 10H, cyclohexyl protons).

Example 27

1-[N-(2-aminophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A mixture of 1.05 g of 1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 2, 2 ml of hydrazine hydrate and 1 g of Raney nickel in 70 ml of methanol was stirred at 50°C for 1.5 h. The insoluble matter was separated off by filtration and the solution was evaporated to dryness. The residue was crystallised from ethanol to give 0.69 g (71%) of the title compound. Melting point: 138.5-140°C.

^{1}H-NMR ($CDCl_3$, δ): 7.15 (dd, 1H, aminophenyl ring CH), 7.10-6.80 (m, 5H, aminophenyl ring CH and methoxyphenyl ring CHs), 6.80-6.65 (m, 2H, aminophenyl ring

CHs), 4.96 (s, 2H, NH_2), 4.96-4.65 (m, 1H, CONC<u>H</u>(H)CH_2N), 3.86 (s, 3H, OCH_3), 3.20-2.80 (m, 7H, CONCH(<u>H</u>)C<u>H</u>$_2$N and piperazine protons), 2.45-2.65 (m, 4H, piperazine protons), 2.10 (tt, 1H, CH(O)), 1.90-0.80 (m, 10H, cyclohexyl protons).

Example 28

1-[N-(2-acetylaminophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A solution of 0.04 ml of acetyl chloride in 0.5 ml of dichloromethane was added at room temperature to a stirred solution of 0.22 g of 1-[N-(2-aminophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 27, and 0.08 ml of triethylamine in 5 ml of dichloromethane. After 2 h stirring at the same temperature, the solvent was evaporated off and the residue was purified by flash chromatography (dichloromethane : acetonitrile 98:2) to give 0.12 g (50%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 9.90 (s, 1H, NH), 7.85 (dd, 1H, acetylaminophenyl ring CH), 7.40 (td, 1H, acetylaminophenyl ring CH), 7.23-7.10 (m, 2H, acetylaminophenyl ring CHs), 7.05-6.80 (m, 4H, methoxyphenyl ring CHs), 5.00-4.80 (m, 1H, CONC<u>H</u>(H)CH_2N), 3.83 (s, 3H, OCH_3), 3.20-2.25 (m, 11H, CONCH(<u>H</u>)C<u>H</u>$_2$N and piperazine protons), 2.15 (s, 3H, $COCH_3$), 2.05-1.85 (m, 1H, CHC(O)), 1.75-0.80 (m, 10H, cyclohexyl protons).

Example 29

1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine N^1-oxide

A suspension of 0.89 g of 83% magnesium monoperoxyphthalate .0.6 H_2O in 10 ml of water was added dropwise into a solution of 1.4 g of 1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 2, in 10 ml of chloroform and 45 ml of methanol at 5°C. After overnight resting at room temperature, the solvents were evaporated off. The residue was taken up in 50 ml of water, alkalinised with 20% sodium carbonate and extracted with chloroform. The organic phase was dried on anhydrous sodium sulphate and evaporated to dryness. The residue was purified by flash chromatography (chloroform : 2N methanolic ammonia, gradient 100:7 to 100:20) to give 0.5 g of a crude. Crystallisation from acetone yielded 0.35 g (24%) of the title compound. Melting point: 128-132°C.

^{1}H-NMR ($CDCl_3$, δ): 8.05 (dd, 1H, nitrophenyl ring H3), 7.70 (ddd, 1H, nitrophenyl ring H5), 7.50 (ddd, 1H, nitrophenyl ring H4), 7.41 (dd, 1H, nitrophenyl ring H6), 7.07-6.76 (m, 4H, methoxyphenyl ring CHs), 4.40-4.12 (m, 2H, CONC<u>H</u>$_2$C<u>H</u>$_2$N), 3.85 (s, 3H, OCH_3), 3.70-3.35 (m, 6H, CONC<u>H</u>$_2$C<u>H</u>$_2$N and piperazine protons), 3.35-3.07 (m, 4H, piperazine protons), 2.05-1.80 (m, 1H, CHC(O)), 1.75-0.75 (m, 10H, cyclohexyl protons).

Example 30

1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine N^4-oxide

The title compound was isolated during purification of the compound described in Example 29. Yield 0.23 g (16%) as a vitreous solid.

^{1}H-NMR ($CDCl_3$, δ): 8.75 (dd, 1H, methoxyphenyl ring H6), 8.05 (dd, 1H, nitrophenyl ring H3), 7.71 (ddd, 1H, nitrophenyl ring H5), 7.57 (ddd, 1H, nitrophenyl ring H4), 7.47 (dd, 1H, nitrophenyl ring H6), 7.37 (ddd, 1H, methoxyphenyl ring H4 (H5)), 7.10 (ddd, 1H, methoxyphenyl ring H5 (H4)), 6.98 (dd, 1H, methoxyphenyl ring H3), 4.72-4.41 (m, 2H, piperazine protons), 4.03 (s, 3H, OCH_3), 3.83 (t, 2H, $CONCH_2CH_2N$), 3.35-3.09 (m, 2H, piperazine protons), 2.98-2.77 (m, 2H, $CONCH_2CH_2N$), 2.77-2.30 (m, 4H, piperazine protons), 2.05-0.83 (m, 11H, cyclohexyl protons).

Example 31

1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine N^1,N^4-dioxide

The title compound was synthesised as described in Example 29 but using equimolar amounts of magnesium monoperoxyphthalate and 1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine. Yield 43% after crystallisation from acetonitrile. Melting point: 153-157°C.

^{1}H-NMR ($CDCl_3$, δ): 8.70 (dd, 1H, methoxyphenyl ring H6), 8.05 (dd, 1H, nitrophenyl ring H3), 7.70 (ddd, 1H, nitrophenyl ring H5), 7.58 (ddd, 1H, nitrophenyl ring H4), 7.49-7.32 (m, 2H, nitrophenyl ring H6 and methoxyphenyl ring H4), 7.13 (ddd, 1H, methoxyphenyl ring H5), 7.00 (dd, 1H, methoxyphenyl ring H3), 5.92-5.67 (m, 2H, piperazine protons), 4.70-4.45 (m, 2H, piperazine protons), 4.45-4.05 (m, 2H, $CONCH_2CH_2N$), 4.00 (s, 2H, $CONCH_2CH_2N$), 3.30-3.08 (m, 2H, piperazine protons), 3.05-2.85 (m, 2H, piperazine protons), 2.05-1.78 (m, 1H, CHC(O)), 1.78-0.70 (m, 10H, cyclohexyl protons).

Example 32

1-[N-(2-nitrophenyl)-N-(3-furylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A suspension of 0.77 g of the monohydrochloride of 1-[N-(2-nitrophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 1 in 50 ml of toluene was stirred at reflux removing about 20 ml of distillate. After cooling to 60-70°C, 0.9 ml of 97% diisopropylethylamine (DIPEA) was added and the mixture was stirred for 15 minutes. 0.66 g of 3-furylcarbonyl chloride was then added. The mixture was stirred at reflux for 5 h. cooled to room temperature. washed sequentially with water. 1N sodium

hydroxide and water, dried on anhydrous sodium sulphate and evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate : petroleum ether, gradient 1:1 to 7:3) affording 0.67 g (75%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 8.05 (dd, 1H, nitrophenyl ring H3), 7.73-7.58 (m, 2H, nitrophenyl ring H5 and H6), 7.58-7.45 (m, 1H, nitrophenyl ring H4), 7.15 (bs, 1H, furan ring H2), 7.02-6.77 (m, 5H, furan ring H5 and methoxyphenyl ring CHs), 6.13 (bs, 1H, furan ring H4), 4.30-4.08 (m, 1H, CONCH(H)CH_2N), 3.90-3.70 (m, 1H, CONCH(H)CH_2N), 3.83 (s, 3H,OCH_3), 3.05-2.80 (m, 4H, piperazine protons), 2.80-2.62 (m, 2H, $CONCH_2CH_2N$), 2.62-2.45 (m, 4H, piperazine protons).

Example 33

1-[N-(2-nitrophenyl)-N-(2-furylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 32, but using 2-furylcarbonyl chloride in place of 3-furylcarbonyl chloride. Yield 77%.

^{1}H-NMR ($CDCl_3$, δ): 8.05 (dd, 1H, nitrophenyl ring H3), 7.72-7.45 (m, 3H, other nitrophenyl ring CHs), 7.20 (bs, 1H, furan ring H3), 7.05-6.75 (m, 4H, methoxyphenyl ring CHs), 6.49 (bs, 1H, furan ring H4), 6.25 (bs, 1H, furan ring H5), 4.30-4.10 (m, 1H, CONCH(H)CH_2N), 3.98-3.75 (m, 1H, CONCH(H)CH_2N), 3.83 (s, 3H,OCH_3), 3.15-2.85 (m, 4H, piperazine protons), 2.85-2.65 (m, 2H, $CONCH_2CH_2N$), 2.65-2.48 (m, 4H, piperazine protons).

Example 34

1-[N-(2-nitrophenyl)-N-(2-thienylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 32, but using 2-thienylcarbonyl chloride in place of 3-furylcarbonyl chloride and refluxing for 8 h. Yield 59%.

^{1}H-NMR ($CDCl_3$, δ): 8.03 (dd, 1H, nitrophenyl ring H3), 7.71-7.60 (m, 2H, nitrophenyl ring H5 and H6), 7.60-7.45 (m, 1H, nitrophenyl ring H4), 7.27 (dd, 1H, thiophen ring H3 (H5)), 7.05-6.70 (m, 6H, thiophen H4 and H5 (H3) and methoxyphenyl ring CHs), 4.22-4.10 (m, 1H, CONCH(H)CH_2N), 3.92-3.71 (m, 1H, CONCH(H)CH_2N), 3.80 (s, 3H,OCH_3), 3.10-2.80 (m, 4H, piperazine protons), 2.80-2.65 (m, 2H, $CONCH_2CH_2N$), 2.65-2.45 (m, 4H, piperazine protons).

Example 35

1-[N-(2-nitrophenyl)-N-(3-thienylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 32, but using 3-thienylcarbonyl chloride in place of 3-furylcarbonyl chloride and refluxing for 7 h. Yield 88%.

^{1}H-NMR ($CDCl_3$, δ): 7.93 (dd, 1H, nitrophenyl ring H3), 7.70-7.55 (m, 2H, nitrophenyl ring H5 and H6), 7.48-7.35 (m, 1H, nitrophenyl ring H4), 7.25-7.12 (m, 1H, thiophen ring H2), 7.12-7.02 (m, 1H, thiophen ring H5) 7.02-6.91 (m, 1H, thiophen ring H4), 6.91-6.78 (m, 4H, methoxyphenyl ring CHs), 4.32-4.10 (m, 1H, CONC<u>H</u>(H)CH_2N), 3.90-3.70 (m, 1H, CONCH(<u>H</u>)CH_2N), 3.81 (s, 3H,OCH_3), 3.05-2.78 (m, 4H, piperazine protons), 2.78-2.65 (m, 2H, $CONCH_2C\underline{H}_2N$), 2.65-2.45 (m, 4H, piperazine protons).

Example 36

1-[N-(2-nitrophenyl)-N-(4-pyridylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 32, but using 4-pyridylcarbonyl chloride in place of 3-furylcarbonyl chloride and refluxing for 14 h. The crude was purified by flash chromatography (chloroform : 2.5N methanolic ammonia, gradient 100:1.5 to 100:3). Yield 39%.

^{1}H-NMR ($CDCl_3$, δ): 8.42 (dd, 2H, pyridine ring H2 and H6). 7.90 (dd, 1H, nitrophenyl ring H3), 7.62-7.45 (m, 2H, nitrophenyl ring H5 and H6). 7.45-7.30 (m, 1H, nitrophenyl ring H4), 7.15 (dd, 2H, pyridine ring H3 and H5) 7.08-6.75 (m, 4H, methoxyphenyl ring CHs), 4.50-4.20 (m, 1H, CONC<u>H</u>(H)CH_2N), 3.90-3.65 (m, 1H. CONCH(<u>H</u>)CH_2N), 3.80 (s, 3H,OCH_3), 3.15-2.28 (m, 10H, $CONCH_2C\underline{H}_2N$ and piperazine protons).

Example 37

1-[N-(2-nitrophenyl)-N-(3-pyridylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 32, but using 3-pyridylcarbonyl chloride in place of 3-furylcarbonyl chloride and refluxing for 12 h. The crude was purified by flash chromatography (chloroform : 2.5N methanolic ammonia 100:3). Yield 46%.

^{1}H-NMR ($CDCl_3$, δ): 8.50-8.35 (m, 2H, pyridine ring H2 and H6), 7.90 (dd, 1H, nitrophenyl ring H3), 7.72 (dd, 1H, pyridine ring H4), 7.60-7.50 (m, 2H, nitrophenyl ring H5 and H6), 7.43-7.28 (m, 1H, nitrophenyl ring H4) 7.30-7.15 (m, 1H, pyridine ring H5), 7.03-6.76 (m, 4H, methoxyphenyl ring CHs), 4.35-4.15 (m, 1H, CONC<u>H</u>(H)CH_2N), 4.00-3.75 (m, 1H, CONCH(<u>H</u>)CH_2N), 3.80 (s, 3H,OCH_3), 3.10-2.40 (m, 10H, $CONCH_2C\underline{H}_2N$ and piperazine protons).

Example 38

1-[N-(2-nitrophenyl)-N-(2-pyrazinylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described Example 32, but using 2-pyrazinylcarbonyl chloride in place of 3-furylcarbonyl chloride and refluxing for 1 h. The crude was purified by flash chromatography (chloroform : 2.5N methanolic ammonia, gradient 100:1 to 100:3). Yield 89%.

^{1}H-NMR ($CDCl_3$, δ): 9.08 (d, 1H, pyrazine ring H3), 8.40 (d, 1H, pyrazine ring H6), 8.07 (d, 1H, pyrazine ring H5), 7.97 (dd, 1H, nitrophenyl ring H3), 7.62-7.50 (m, 2H, nitrophenyl ring H5 and H6) 7.48-7.31 (m, 1H, nitrophenyl ring H4), 7.05-6.80 (m, 4H, methoxyphenyl ring CHs), 4.31-4.15 (m, 1H, CONC<u>H</u>(H)CH_2N), 4.08-3.92 (m, 1H, CONCH(<u>H</u>)CH_2N), 3.82 (s, 3H,OCH_3), 3.05-2.40 (m, 10H, CONCH_2C<u>H</u>$_2$N and piperazine protons).

Example 39

1-[N-(2-nitrophenyl)-N-(1-methylcyclohexylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

Operating as described in the first step of Example 26, but using 1-methylcyclohexylcarbonyl chloride [J. Org. Chem. 47, 3242 (1982)] in place of cyclohexylcarbonyl chloride and refluxing for 50 h, gave crude 1-methyl-N-(2-nitrophenyl)-cyclohexylcarboxamide. This was purified by flash chromatography (petroleum ether : ethyl acetate 100:2). Yield 90%.

^{1}H-NMR ($CDCl_3$, δ): 10.75 (s, 1H, NH), 8.85 (dd, 1H, nitrophenyl ring H6), 8.22 (dd, 1H, nitrophenyl ring H3), 7.62 (ddd, 1H, nitrophenyl ring H5), 7.15 (ddd, 1H, nitrophenyl ring H4) 2.20-1.95 (m, 2H, cyclohexyl protons), 1.75-1.35 (m, 8H, cyclohexyl protons), 1.25 (s, 3H, CH_3).

A mixture of 0.3 g of 1-methyl-N-(2-nitrophenyl)-cyclohexylcarboxamide, prepared as above described, 50 ml of toluene and 0.26 g of potassium t-butoxide was stirred at reflux, removing about 11 ml of distillate. A solution of 0.32 g of 1-(2-chloroethyl)-4-(2-methoxyphenyl)-piperazine in 10 ml of toluene was then added to the mixture. After 16 h stirring at reflux, the mixture was cooled and washed with water. The organic layer was dried on anhydrous sodium sulphate and evaporated to dryness. The crude was purified by flash chromatography (petroleum ether : ethyl acetate 7:3) to give 0.51 g (43%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 7.98 (dd, 1H, nitrophenyl ring H3), 7.40 (ddd, 1H, nitrophenyl ring H5), 7.08-6.80 (m, 6H, nitrophenyl ring H4 and H6 and methoxyphenyl ring CHs), 4.31-4.10 (m, 2H, CONC<u>H</u>$_2$$CH_2$), 3.85 (s, 3H, OCH_3), 3.20-2.98 (m, 4H, piperazine protons), 2.88-2.62 (m, 6H, CONCH_2C<u>H</u>$_2$ and piperazine protons), 1.90-1.70 (m, 2H, cyclohexyl protons), 1.53-1.22 (m, 8H, cyclohexyl protons), 1.18 (s, 3H, CH_3).

Example 40

1-[N-(2-nitrophenyl)-N-(1-phenylcyclohexylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

1-phenyl-N-(2-nitrophenyl)-cyclohexylcarboxamide was prepared following the procedure described in the first step of Example 39, except that 1-phenylcyclohexylcarbonyl chloride [J. Am. Chem. Soc. 68, 2345-7 (1946)] was used in place of 1-methylcyclohexylcarbonyl chloride, toluene was used in place of dichloromethane, DIPEA was used in place of triethylamine and the reaction mixture was refluxed for 15 h. The crude was purified by flash chromatography (petroleum ether : ethyl acetate 98:2). Yield 91%.

^{1}H-NMR ($CDCl_3$, δ): 10.32 (s, 1H, NH), 8.76 (dd, 1H, nitrophenyl ring H6), 8.12 (dd, 1H, nitrophenyl ring H3), 7.64-7.32 (m, 5H, phenyl ring CHs), 7.28 (ddd, 1H, nitrophenyl ring H5), 7.08 (ddd, 1H, nitrophenyl ring H4), 2.54-2.34 (m, 2H, cyclohexyl protons), 2.22-2.02 (m, 2H, cyclohexyl protons), 1.76-1.28 (m, 6H, cyclohexyl protons).

The title compound was prepared as described in the second step of Example 39, except that 1-phenyl-N-(2-nitrophenyl)-cyclohexylcarboxamide was used in place of 1-methyl-N-(2-nitrophenyl)-cyclohexylcarboxamide and refluxing lasted 22 h. The crude was purified by flash chromatography (petroleum ether : ethyl acetate, gradient 8:2 to 7:3). Yield 37%.

^{1}H-NMR ($CDCl_3$, δ): 7.90 (dd, 1H, nitrophenyl ring H3), 7.45-7.10 (m, 7H, phenyl ring CHs and nitrophenyl ring H5 and H6), 7.04-6.78 (m, 5H, nitrophenyl ring H4 and methoxyphenyl ring CHs), 4.30-4.12 (m, 2H, $CONCH_2CH_2$), 3.82 (s, 3H, OCH_3), 3.18-2.93 (m, 4H, piperazine protons), 2.80-2.50 (m, 6H, $CONCH_2CH_2$ and piperazine protons), 2.30-2.10 (m, 2H, cyclohexyl protons), 1.92-1.75 (m, 2H, cyclohexyl protons), 1.74-1.35 (m, 6H, cyclohexyl protons).

Example 41

1-[N-[2-(2,2,2-trifluoroethoxy)-phenyl]-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 3, except that 2-(2,2,2-trifluoroethoxy)aniline (EP 748800) was used in place of 2-trifluoromethoxyaniline and the reaction mixture was refluxed for 7 h. The crude was purified by flash chromatography (petroleum ether : ethyl acetate, gradient 9:1 to 8:2). Yield 38%.

^{1}H-NMR ($CDCl_3$, δ): 7.08-6.80 (m, 5H, methoxyphenyl ring CHs and trifluoroethoxyphenyl ring CH), 6.80-6.57 (m, 3H, trifluoroethoxyphenyl ring CHs), 5.11-4.70 (m, 1H, NH), 4.35 (q, 2H, OCH_2CF_3), 3.85 (s, 3H, OCH_3), 3.38-3.19 (m, 2H, $NHCH_2CH_2$), 3.19-2.98 (m, 4H, piperazine protons), 2.88-2.60 (m, 6H, $NHCH_2CH_2$ and piperazine protons).

Example 42

1-[N-[2-(2,2,2-trifluoroethoxy)-phenyl]-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine

A mixture of 0.41 g of 1-[N-[2-(2,2,2-trifluoroethoxy)-phenyl]-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in example 41, 5.4 ml of 97% DIPEA, and 3.9 ml of cyclohexylcarbonyl chloride in 30 ml of toluene was stirred at reflux for 10 h. After cooling to room temperature, the mixture was washed sequentially with water, 1N sodium hydroxide and water. The organic layer was dried on anhydrous sodium sulphate and evaporated to dryness. The crude was purified by flash chromatography (petroleum ether : ethyl acetate 1:1) followed by crystallisation from diethyl ether to give 0.2 g (37%) of the title compound. Melting point: 109.6-112°C.

^{1}H-NMR ($CDCl_3$, δ): 7.42-7.22 (m, 2H, trifluoroethoxyphenyl ring CHs), 7.15-6.77 (m, 6H, trifluoroethoxyphenyl ring CHs and methoxyphenyl ring CHs), 4.38 (q, 2H, OCH_2CF_3), 4.22-402 (m, 1H, CONCH(H)CH_2N), 3.82 (s, 3H, OCH_3), 3.58-3.39 (m, 1H, CONCH(H)CH_2N), 3.15-2.90 (m, 4H, piperazine protons), 2.80-2.45 (m, 6H, CONCH$_2$CH_2N and piperazine protons), 2.05-1.88 (m, 1H, CHC(O)), 1.75-0.80 (m, 10H, cyclohexyl protons).

Example 43

1-[N-(2-cyanophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine hydrochloride

N-(2-cyanophenyl)-cyclohexylcarboxamide was prepared following the procedure described in the first step of Example 26, except that 2-cyanoaniline was used in place of 2-trifluoromethylaniline. Yield 75%. M.p. 135-137°C.

^{1}H-NMR ($CDCl_3$, δ): 8.40 (dd, 1H, cyanophenyl ring H3), 7.70-7.50 (m, 3H, cyanophenyl ring H5 and H6 and NH), 7.12 (ddd, 1H, cyanophenyl ring H4), 2.30 (tt, 1H, CHC(O)), 2.05-1.10 (m, 10H, cyclohexyl protons).

The title compound was prepared following the procedure described in the second step of Example 39, except that N-(2-cyanophenyl)-cyclohexylcarboxamide, prepared as above described, was used in place of 1-methyl-N-(2-nitrophenyl)-cyclohexylcarboxamide and reflux lasted 1 h. The crude was purified by flash chromatography (dichloromethane : methanol 98:2). The residue was dissolved in acetone and ethereal hydrogen chloride, was added. The solution was evaporated to dryness, and crystallised from acetone : diethyl ether to give the title compound. Yield 7%.

^{1}H-NMR (DMSO-d_6, δ): 11.28-11.07 (br, 1H, NH^+), 8.05 (dd, 1H, cyanophenyl ring H6), 7.92-7.80 (m, 2H, cyanophenyl ring CHs), 7.72-7.60 (m, 1H, cyanophenyl ring CH), 7.05-6.82 (m, 4H, methoxyphenyl ring CHs), 4.45-4.30 (m, 1H, CONCH(H)CH_2N), 3.92-3.75 (m, 1H, CONCH(H)CH_2N), 3.80 (s, 3H, OCH_3), 3.70-3.40 (m, 4H, piperazine protons).

3.40-3.00 (m, 6H, $CONCH_2\underline{CH_2}N$ and piperazine protons), 1.98-1.80 (m, 1H, CHC(O)), 1.80-0.75 (m, 10H, cyclohexyl protons).

Example 44

1-[N-(2-nitrophenyl)-1-amino-2-propyl]-4-(2-methoxyphenyl)-piperazine

A mixture of 1 g of 1-(2-methoxyphenyl)-piperazine, 0.57 g of 2-chloropropionamide, 1 ml of DIPEA and 5 ml of toluene was stirred at reflux for 3 h under nitrogen. After cooling to room temperature the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried on anhydrous sodium sulphate and the solvents were evaporated off. The residue was purified by flash chromatography (dichloromethane : 2N methanolic ammonia 95:5) to give 0.88 g (63%) of 2-[4-(2-methoxyphenyl)-1-piperazinyl]-propionamide.

^{1}H-NMR ($CDCl_3$, δ): 7.25-7.10 (br, 1H, $CON\underline{H}(H)$), 7.10-6.80 (m, 4H, methoxyphenyl ring CHs), 5.75-5.60 (br, 1H, $CONH(\underline{H})$), 3.85 (s, 3H, OCH_3), 3.20-3.00 (m, 5H, piperazine protons, $NC\underline{H}(CH_3)CO$), 2.85-2.60 (m, 4H, piperazine protons), 1.30 (d, 3H, $NCH(C\underline{H_3})CO$).

2 ml of a 2M solution of diborane dimethylsulphide in tetrahydrofuran was added dropwise to a solution of 0.28 g of 2-[4-(2-methoxyphenyl)-1-piperazinyl]-propionamide, prepared as above described, in 7 ml of tetrahydrofuran stirred at -4°C under nitrogen. The mixture was refluxed for 6.5 h, and then 3 ml of methanol was added. The solvents were evaporated off and the residue was taken up in water. The organic phase, obtained by extraction with ethyl acetate, was dried on anhydrous sodium sulphate and evaporated to dryness. The residue was purified by flash chromatography (dichloromethane : 2N methanolic ammonia 95:5) to give 0.07 g (24%) of 2-[4-(2-methoxyphenyl)-1-piperazinyl]-propylamine.

^{1}H-NMR ($CDCl_3$, δ): 7.10-6.80 (m, 4H, methoxyphenyl ring CHs), 3.85 (s, 3H, OCH_3), 3.20-2.90 (m, 4H, piperazine protons), 2.85-2.50 (m, 7H, piperazine protons and $NC\underline{H}(CH_3)C\underline{H_2}$), 2.05-1.85 (br, 2H, NH_2), 0.95 (d, 3H, CH_3).

A mixture of 0.08 g of 2-[4-(2-methoxyphenyl)-1-piperazinyl]-propylamine, prepared as above described, 0.03 ml of 2-nitrofluorobenzene, 0.3 ml of DIPEA and 5 ml of DMF was stirred at 140°C for 3 h under nitrogen. The cooled mixture was diluted with water and extracted with diethyl ether. The organic phase was dried on anhydrous sodium sulphate and evaporated to dryness. The residue was purified by flash chromatography (petroleum ether : ethyl acetate 8:2) to give 0.07 g (62%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 8.90-8.70 (br, 1H, NH), 8.15 (dd, 1H, nitrophenyl ring H3), 7.40 (ddd, 1H, nitrophenyl ring H5), 7.15-6.70 (m, 5H, nitrophenyl ring H6 and methoxyphenyl ring CHs), 6.63 (ddd, 1H, nitrophenyl ring H4), 3.85 (s, 3H, OCH_3), 3.70-2.60 (m, 11H, piperazine protons and $NHC\underline{H_2}C\underline{H}(CH_3)$), 1.10 (d, 3H, CH_3).

Example 45

1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-1-amino-2-propyl]-4-(2-methoxyphenyl)-piperazine

The title compound was prepared following the procedure described in Example 4, except that 1-[N-(2-nitrophenyl)-1-amino-2-propyl]-4-(2-methoxyphenyl)-piperazine, prepared as described in Example 44, was used in place of 1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine, toluene was used instead of 1,2-dichloroethane, and the mixture was heated for 13 h at reflux. The mixture was purified by flash chromatography (petroleum ether : ethyl acetate 1:1). Yield: 61%.

^{1}H-NMR ($CDCl_3$, δ): 8.05 (dd, 1H, nitrophenyl ring H3), 7.85-7.45 (m, 3H, nitrophenyl ring H4, H5 and H6), 7.10-6.75 (m, 4H, methoxyphenyl ring CHs), 3.85 (s, 3H, OCH_3), 3.90-3.75 (m, 1H, CONCH(H)CH(CH_3)), 3.65-2.30 (m, 10H, piperazine protons and CONCH(H)CH(CH_3)), 2.10-1.80 (m, 1H, CHC(O)), 1.80-0.80 (m, 13H, cyclohexyl protons and CH_3).

Example 46

Effects on Volume-Induced Rhythmic Bladder Voiding Contractions in Anaesthetised Rats

A. Methods:

Female Sprague Dawley rats weighing 225-275 g (Crl: CDo BR, Charles River Italia) were used. The animals were housed with free access to food and water and were maintained on a forced 12 h alternating light-dark cycle at 22-24°C for at least one week, except during the experiment. The activity on the rhythmic bladder voiding contractions was evaluated according to the method of Dray (J. Pharmacol. Methods, 13:157, 1985), with some modifications as in Guarneri (Pharmacol. Res., 27:173, 1993). Briefly, rats were anaesthetised by subcutaneous injection of 1.25 g/kg (5 ml/kg) urethane, after which the urinary bladder was catheterised via the urethra using PE 50 polyethylene tubing filled with physiological saline. The catheter was tied in place with a ligature around the external urethral orifice and was connected with conventional pressure transducers (Statham P23 ID/P23 XL). The intravesical pressure was displayed continuously on a chart recorder (Battaglia Rangoni KV 135 with DCI/TI amplifier). The bladder was then filled via the recording catheter by incremental volumes of warm (37°C) saline until reflex bladder voiding contractions occurred (usually 0.8-1.5 ml). For intravenous (i.v.) injection of bioactive compounds, PE 50 polyethylene tubing filled with physiological saline was inserted into the jugular vein.

From the cystometrogram, the number of contractions recorded 15 min before (basal values) and after treatment, as well as the mean amplitude of these contractions (mean height of the peaks in mmHg) was evaluated.

Since most compounds produced an effect that was relatively rapid in onset and led to a complete cessation of bladder contractions, bioactivity was conveniently estimated by measuring the duration of bladder quiescence (i.e., the duration of time during which no contractions occurred). The number of animals tested showing a reduction in the number of contractions >30% of that observed in the basal period was also recorded.

To compare the potency of the tested compounds for inhibiting bladder voiding contractions, equieffective doses which resulted in a contraction disappearance time of 10 minutes (ED_{10min}) were computed by means of least square linear regression analysis. Also computed in this manner were extrapolated doses which induced a reduction of the number of contractions of greater than 30% in 50% of treated rats (ED_{50}, frequency) by the method of Bliss (Bliss C.I., Quart. J. Pharm. Pharmacol. 11, 192-216, 1938). After the suppressive effects of drug injection wore off, the height of the contractile peaks was compared with the height of the peaks previously recorded after the control intravenous administration of vehicle. The potency of the tested compounds (ED_{50} value: the extrapolated doses inducing a 30% reduction of amplitude of the contractions in 50% of treated rats) was evaluated on a quantal basis by the method of Bliss (Bliss C.I., Quart. J. Pharm. Pharmacol. 11, 192-216, 1938).

B. Results

The rapid distension of the urinary bladder in urethane-anaesthetised rats produced a series of rhythmic bladder voiding contractions whose characteristics have been described and are well-known in the art (Maggi et al., Brain Res., 380:83, 1986; Maggi, et al., J. Pharmacol. Exp. Ther., 230:500, 1984). The frequency of these contractions is related to the sensory afferent arm of reflex micturition and to the integrity of the micturition centre, while their amplitude is a property of the efferent arm of the reflex. In this model system, compounds that act mainly on the CNS (such as morphine) cause a block in voiding contraction, whereas drugs that act at the level of the detrusor muscle, such as oxybutynin, lower the amplitude of the bladder contractions.

The results obtained after administration of prior art compounds and compounds of the invention are shown in Table 1.

Compound A, a prior art compound, was more potent than flavoxate and oxybutynin in inhibiting voiding contractions. This compound, in contrast to oxybutynin, did not affect the amplitude of the contraction, indicating no impairment of bladder contractility.

Surprisingly, however, compounds with substituents (e.g. NO_2) at position 2 of the aniline ring in Formula I, such as the compound of Example 2, have significantly higher potency

than unsubstituted compound A, particular with regard to the ED_{10min} values. Like compound A, the compound of Example 2 does not affect bladder contractility. The comparative compounds B and C, with the nitro group at position 3 and 4 of the phenyl ring respectively, showed no pharmacological activity.

Similar results (i.e. higher potency for the 2-substituted derivatives) were obtained for the compounds in which R = H. Thus compounds AA, D and E, which are unsubstituted and 3- and 4-substituted compounds with R = H, are clearly inferior to the compounds of Examples 1, 10 and 11 and 18, i.e., 2-NO_2, 2-CN, 2-$COCH_3$ and 2-$COOCH_3$ derivatives. The compounds of the invention were clearly superior, particularly with regard to the ED_{50} values which are indicators of urinary frequency.

TABLE 1

Effects on rhythmic bladder voiding contractions after intravenous administration. *Data represent the ED_{10min} values (the extrapolated dose inducing 10 min of disappearance of the contractions); the ED_{50} values (the extrapolated doses inducing a reduction of the number of contractions >30% in 50% of treated rats) (frequency), and the ED_{50} values (the extrapolated doses inducing 30% reduction of amplitude of the contractions in 50% of treated rats) (amplitude).*

Compound	ED_{10min} µg/kg	ED50 (frequency) µg/kg	ED50(amplitude) µg/kg
Compound A	650	33	n.a.
Compound B	>1000	>1000	n.a.
Compound C	>1000	>1000	n.a.
Compound D	>1000	>1000	n.a.
Compound E	>1000	>1000	n.a.
Compound AA	663	244	n.a.
Example 1	192	55	n.a.
Example 2	60	9	n.a.
Example 10	122	28	n.a.
Example 11	318	40	n.a.
Example 13	266	29	n.a.
Example 18	101	17	n.a.
Example 20	97	25	n.a.
Example 23	93	18	n.a.
Example 27	131	13	n.a.
Flavoxate	>10000	2648	n.a.
Oxybutinin	7770	>10000	240

n.a. = not active; no significant reduction of the height of peaks

Compound A

1-(N-phenyl-N-cyclohexylcarbonyl-2-aminoethyl)-4-(2-methoxyphenyl)-piperazine.

Compound AA

1-(N-phenyl-2-aminoethyl)-4-(2-methoxyphenyl)-piperazine.

Compound B

1-[N-(3-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine.

Compound C

1-[N-(4-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine.

Compound D

1-[N-(3-nitrophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine.

Compound E

1-[N-(4-nitrophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine.

Example 47

Effects on Cystometric Parameters in Conscious Rats

A. Methods:

Male Sprague Dawley rats (Crl: CDo BR) weighing 250-350 g were used. The animals were housed with free access to food and water and maintained on a forced 12 h alternating light-dark cycle at 22-24°C for at least one week, except during performance of the experiment. To quantify urodynamic parameters in conscious rats, cystometrographic studies were performed using procedures previously described (Guarneri et al., Pharmacol. Res., 24:175, 1991). Male rats were anaesthetised with nembutal (30 mg/kg) and chloral hydrate (125 mg/kg) i.p. and were placed in a supine position. An approximately 10 mm long midline incision was made in the shaved and cleaned abdominal wall. The urinary bladder was gently freed from adhering tissues, emptied, and then cannulated, via an incision at the dome, with a polyethylene cannula (Portex PP30), which was permanently sutured with silk thread. The cannula was exteriorized through a subcutaneous tunnel in the retroscapular area, where it was connected with a plastic adapter to avoid the risk of removal by the animal. For intravenous (i.v.) injection of test compounds, a PE 50 polyethylene tubing filled with physiological saline was inserted into the jugular vein and exteriorized in the retroscapular area. The rats were utilised exclusively one day after implantation. On the day of the experiment, the rats were placed in Bollman's cages; after a stabilisation period of 20 min, and the free tip of the bladder catheter was connected through a T-shaped tube to a pressure transducer (Bentley T 800/Marb P 82) and to a peristaltic pump (Gilson minipuls 2) for a continuous infusion, at the constant rate of 0.1 ml/min, of saline solution into the urinary bladder. The intraluminal pressure signal during infusion was continuously recorded on a polygraph (Battaglia Rangoni KO 380 with ADCl/T amplifier).

Two urodynamic parameters were evaluated: bladder volume capacity (BVC) and micturition pressure (MP). BVC (in ml) is defined as the minimum volume infused after which detrusor contraction (followed by micturition) occurs. MP (in mm Hg) is defined as the maximal intravesical pressure induced by the contraction of detrusor during micturition. Basal BVC and MP values were calculated as the means of the first two recorded cystometrograms. At this point in the assay, the infusion was interrupted and the test compounds were administered. Fifteen minutes after intravenous administration two additional cystometrograms were recorded in each animal and the mean values of the two cystometrographic parameters were calculated. The statistical significance of the differences in urodynamic parameter values was evaluated by Student's t test for paired data.

B. Results:

The effects of different doses of the tested compounds are shown in Table 2. Compound A behaved similarly to flavoxate by increasing BVC. Neither compound impaired bladder contractility, since no consistent changes in MP were observed. In contrast, oxybutynin markedly and dose-dependently decreased MP without effects on BVC. The compound of Example 2 was more potent than compound A and flavoxate; a significant increase in BVC was observed after the i.v. administration of 0.3 mg/kg of the compound of Example 2, compared with the requirement for administration of 1.0 mg/kg of flavoxate or compound A. The compound of Example 2 induced a slight, albeit significant, decrease in MP. This effect, however, was not dose-dependent and was markedly lower than that induced by oxybutynin.

TABLE 2

Effects on cystometrogram in conscious rats.

Data represent mean values ± S.E. of bladder volume capacity (BVC; ml) and of micturition pressure (MP; mmHg), before and 15 min after i.v. injection of the compounds.

COMPOUND	Dose µg/kg	BVC before	BVC after treat.	% of change
Compound A	300	0.81 ± 0.05	0.87 ± 0.05	+ 7.4
	1000	0.78 ± 0.11	0.97 ± 0.11 **	+ 24.4
Example 2	300	0.71 ± 0.09	0.87 ± 0.10 *	+ 22.5
	1000	0.62 ± 0.09	0.75 ± 0.10 **	+ 21.0
Example 8	300	0.59 ± 0.04	0.71 ± 0.05 *	+ 21.0
	1000	0.65 ± 0.10	0.88 ± 0.12 **	+ 35.0
FLAVOXATE	300	0.76 ± 0.11	0.87 ± 0.11	+ 14.5
	1000	0.88 ± 0.15	1.11 ± 0.16 **	+ 26.1
OXYBUTYNIN	100	0.82 ± 0.15	0.89 ± 0.18	+ 8.5
	300	0.83 ± 0.13	0.83 ± 0.12	± 0.0
	1000	0.94 ± 0.19	1.00 ± 0.18	± 6.4

COMPOUND	Dose µg/kg	MP before	MP after treat.	% of change
Compound A	300	90.6 ± 10.4	85.6 ± 11.3	- 5.5
	1000	90.2 ± 6.5	84.1 ± 5.2	- 6.8
Example 2	300	95.4 ± 6.4	80.4 ± 6.5 **	- 15.7
	1000	109.0 ± 12.1	99.6 ± 11.2 *	- 8.6
Example 8	300	116.1 ±17.4	98.3 ± 17.2 **	- 15.0
	1000	81.3 ± 9.0	64.8 ± 10.5 *	- 20.0
FLAVOXATE	300	89.2 ± 10.7	95.0 ± 10.9	+ 6.5
	1000	90.4 ± 10.7	80.1 ± 11.1	- 11.4
OXYBUTYNIN	100	95.2 ± 9.2	77.4 ± 10.3 **	- 18.7
	300	82.3 ± 8.7	50.5 ± 6.3 **	- 38.6

*=P<0.05, **=P<0.01 versus basal values; Student's t test for paired data

Example 48 : Radioreceptor Binding to 5-HT_{1A} and other different neurotransmitter binding sites.

A. Methods:

Recombinant human $5HT_{1A}$ receptors:

Genomic clone G-21 coding for the human 5-HT_{1A} serotonergic receptor is stably transfected in a human cell line (HeLa). HeLa cells were grown as monolayers in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10 % fetal calf serum and gentamicin (100 mg/ml), 5% CO_2 at 37°C. Cells were detached from the growth flask at 95% confluence by a cell scraper and were lysed in ice-cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4). Homogenates were centrifuged at 40000 x g x 20 min and pellets were resuspended in a small volume of ice-cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4) and immediately frozen and stored at -70°C until use. On the day of experiment, cell membranes were resuspended in binding buffer: 50 mM Tris HCl (pH 7.4), 2.5 mM $MgCl_2$, 10μM pargiline (Fargin et al., Nature 335, 358-360, 1988). Membranes were incubated in a final volume of 1 ml for 30 min at 30°C with 0.2 - 1 nM [^{3}H]8-OH-DPAT, in absence or presence of competing drugs; non-specific binding was determined in the presence of 10 μM 5-HT. The incubation was stopped by addition of ice-cold Tris-HCl buffer and rapid filtration through 0.2% polyethyleneimine pretreated Whatman GF/B or Schleicher & Schuell GF52 filters.

Native 5-HT_{2A} serotoninergic receptors and α_2 -adrenoceptors (from animal tissues)

Binding studies on native α_2 adrenergic receptors (Diop L. et al, J. Neurochem. 41, 710-715, 1983), and 5-HT_{2A} serotonergic receptors (Craig A. and Kenneth J., Life Sci. 38, 117-127, 1986) were carried out in membranes of rat cerebral cortex. Male Sprague Dawley rats (200-300g, SD Harlan/Nossan, Italy) were killed by cervical dislocation and cerebral cortexes were excised and immediately frozen in liquid nitrogen and stored at -70°C until use. Tissues were homogenized (2x20 sec) in 50 volumes of cold 50 mM Tris-HCl buffer pH 7.4, using a Polytron homogenizer (speed 7). Homogenates were centrifuged at 49000xg for 10 min, resuspended in 50 volumes of the same buffer, incubated at 37°C for 15 min and centrifuged and resuspended twice more. The final pellets were suspended in 100 volumes of 50 mM Tris-HCl buffer pH 7.4, containing 10μM pargiline and 0.1% ascorbic acid (α_2 adrenergic receptors) or in 100 volumes of 50 mM Tris-HCl buffer pH 7.7 (5-HT_{2A} serotonergic receptors). Membranes were incubated in a final volume of 1 ml for 30 min at 25°C with 0.5-1.5 nM [^{3}H]rauwolscine (α_2-adrenergic receptors) or for 20 min at 37°C with 0.7-1.3 nM [^{3}H]ketanserin (5-HT_{2A} receptors), in absence or presence of competing drugs. Non-specific binding was determined in the presence of 10 μM phentolamine (α_2-adrenergic receptors) or 2 μM ketanserin (5-HT_{2A} serotoninergic receptors). The incubation was stopped by addition of ice-cold 50 mM Tris-HCl buffer and rapid filtration through 0.2% polyethyleneimine

pretreated Whatman GF/B or Schleicher & Schuell GF52 filters. The filters are then washed with ice-cold buffer and the radioactivity retained on the filters was counted by liquid scintillation spectrometry.

B. Results:

The inhibition of specific binding of the radioligands by the tested drugs was analyzed to estimate the IC_{50} value by using the non-linear curve-fitting program Allfit (De Lean et al., Am. J. Physiol. 235, E97-E102, 1978). The IC_{50} value was converted to an affinity constant (Ki) by the equation of Cheng & Prusoff (Cheng, Y.C.; Prusoff, W.H. Biochem. Pharmacol. 22, 3099-3108, 1973).

The results shown in Table 3A demonstrate that compound A and the compound of Example 2 both have a very high affinity for 5-HT_{1A} receptors, but their binding profile is different. The compound of Example 2 was much more selective than compound A for the 5-HT_{1A} receptor *versus* the 5-HT_{2A} and the α_2-adrenoceptors. All the other compounds of the invention tested (Table 3B) had high affinity for the 5-HT_{1A} receptor.

TABLE 3A

Binding affinity for the 5-HT_{1A} receptor and other neurotransmitter binding sites

Data are expressed as Ki (nM).

Compound	5-HT_{1A}	5-HT_{2A}	α_2
Compound A	0.10	629	2625
Example 2	0.05	>10000	>10000
Example 8	0.36	1065	2342
Example 18	0.60	1829	314

TABLE 3B

Binding affinity for the 5-HT_{1A} receptor
Data are expressed as Ki (nM).

Compound	5-HT_{1A}
Ex. 3	10.28
Ex. 4	0.64
Ex. 5	14.85
Ex. 6	0.45
Ex. 7	3.82
Ex. 8	0.36
Ex. 10	17.23
Ex. 11	2.92
Ex. 12	4.77
Ex. 13	0.50
Ex 14	10.32
Ex 15	6.20
Ex. 16	2.90
Ex. 17	20.15
Ex. 18	0.60
Ex. 20	24.62
Ex. 21	2.72
Ex. 22	18.18
Ex. 23	0.14
Ex. 25	8.91
Ex. 26	2.69
Ex. 27	0.57
Ex. 28	18.78
Ex. 30	7.96
Ex. 32	19.36
Ex. 34	16.27
Ex. 35	8.00
Ex. 38	1.02

Measurement of Pre- and Post-Synaptic 5-HT_{1A} Receptor Antagonist Activity

A. Methods:

Antagonism of hypothermia induced by 8-OH-DPAT in mice (pre-synaptic antagonism).

The antagonistic effect of the 5-HT_{1A} receptor antagonists of the invention on hypothermia induced by 8-OH-DPAT was evaluated by the method of Moser (Moser, Eur.J.Pharmacol., 193:165, 1991) with minor modifications as described below. Male CD-1 mice (28-38 g) obtained from Charles River (Italy) were housed in a climate-controlled room (temperature 22 ± 2 C; humidity 55 ± 15%) and maintained on a 12 h light/dark cycle with free access to food and water. On the day of experiment, mice were placed singly in clear plastic boxes under the same ambient conditions. Body temperature was measured by the insertion of a temperature probe (Termist TM-S, LSI) into the rectum to a depth of 2 cm. Rectal temperature was measured immediately prior to intravenous injection of the test

compound. All animals then received 8-OH-DPAT (0.5 mg/kg s.c.) and their temperature was measured 30 min later. For each animal, temperature changes were calculated with respect to pretreatment values and the mean values were calculated for each treatment group. A linear regression equation was used in order to evaluate ID_{50} values, defined as the dose of antagonist needed to block 50% of the hypothermic effect induced by 0.5 mg/kg 8-OH-DPAT administered subcutaneously.

Inhibition of forepaw treading induced by 8-OH-DPAT in rats (post-synaptic antagonism).

The inhibitory effect of 5-HT_{1A} receptor antagonists on the forepaw treading induced in rats by subcutaneous injection of 8-OH-DPAT was evaluated by the method of Tricklebank (Tricklebank et al., Eur. J.Pharmacol., 117:15, 1985) with minor modifications as described below.

Male Sprague-Dawley rats (150-175 g) obtained from Charles River (Italy), were housed in a climate-controlled room and maintained on a 12 h light/dark cycle with free access to food and water. On the day of experiment, rats were placed singly in clear plastic boxes. Rats were treated with reserpine, 1 mg/kg s.c., 18-24 h before the test to deplete intracellular stores of noradrenaline. For evaluation of antagonistic activity, compounds were i.v. administered 16 min before 8-OH-DPAT (1 mg/kg s.c.). Observation sessions of 30 s duration began 3 min after treatment with the agonist and were repeated every 3 min over a period of 15 min. The appearance of the forepaw treading symptom induced by postsynaptic stimulation of the $5HT_{1A}$ receptors was noted, and its intensity was scored using a ranked intensity scale in which: 0 = absent, 1 = equivocal, 2 = present and 3 = intense. Behavioral scores for each treated rat were accumulated over the time course (5 observation periods) and expressed as mean values of 8-10 rats. A linear regression equation was used in order to evaluate ID_{50} values, defined as the dose of antagonist needed to block 50% of the forepaw treading intensity induced by 1 mg/kg 8-OH-DPAT administered subcutaneously.

B. Results:

The results are shown in Table 4. These results demonstrate that compound of Example 2 exhibits significant pre-synaptic and post-synaptic 5-HT_{1A} receptor antagonist activity. Compound A, by contrast, proved at least 10 fold less active than compound of Example 2 in both models.

TABLE 4

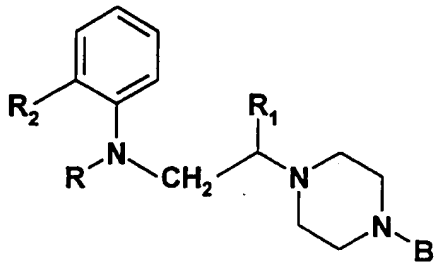
Antagonistic activity for the pre- and post-synaptic 5-HT_{1A} receptor.

Data are expressed as ID_{50} in mg/kg.

Compound	Pre-synaptic 5-HT_{1A} ID_{50}	Post-synaptic 5-HT_{1A} ID_{50}
Compound A	221	350
Example 2	20	36
Example 13	-	82
Example 18	n.a.	84
Example 23	-	177

CLAIMS

1. A compound having the general formula I:



(I)

wherein

R represents a hydrogen atom or an alkylcarbonyl, a cycloalkylcarbonyl, substituted cycloalkylcarbonyl or monocyclic heteroarylcarbonyl group,

R_1 represents a hydrogen atom or a lower alkyl group,

R_2 represents a halogen atom or an alkoxy, phenoxy, nitro, cyano, acyl, amino, acylamino, alkylsulphonylamino, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, acylcarbamoyl, trifluoromethyl or polyfluoroalkoxy group, and

B represents a substituted monocyclic aryl group, a bicyclic aryl group, a substituted bicyclic aryl group, a mono- or bicyclic heteroaryl group, a substituted mono- or bicyclic heteroaryl group or a substituted benzyl group,

with the provisos that:

if both R and R_1 represent hydrogen atoms and R_2 represents a nitro group, then B does not represent a 2-methoxyphenyl, 4-chlorophenyl, 4-hydroxyphenyl, 3-acetylphenyl, 4-sulphamoylphenyl, 3,4,5-trimethoxyphenyl, 2-chloro-4-methylphenyl or 2-pyridyl group;

if both R and R_1 represent hydrogen atoms and R_2 represents a carbamoyl group, then B does not represent a 4-hydroxyphenyl group; and

if B represents an alkoxy substituted aryl group, then the alkoxy group must be at position 2 of the aryl ring;

or an enantiomer, N-oxide, hydrate or pharmaceutically acceptable salt of such a compound.

2. A compound according to claim 1 wherein B represents a 2-methoxyphenyl, 2,5-dichlorobenzyl or 4-indolyl group.

3. A compound according to claim 1 or claim 2 wherein R_2 represents an iodine atom or a methoxy, phenoxy, nitro, cyano, acetyl, amino, acetamido, acetoxycarbonyl, carbamoyl,

ethylcarbamoyl, dimethylcarbamoyl, cyclohexylcarbonylcarbamoyl, trifluoromethyl, trifluoromethoxy or 2-(2,2,2-trifluoro)-ethoxy group.

4. A compound according to any preceding claim wherein R represents a hydrogen atom or a cyclohexylcarbonyl, 1-methylcyclohexylcarbonyl, 1-phenylcyclohexylcarbonyl, 3-furylcarbonyl, 3-thienylcarbonyl, 4-pyridylcarbonyl, 3-pyridylcarbonyl or 2-pyrazinylcarbonyl group.

5. A compound according to any preceding claim wherein R_1 represents a hydrogen atom or a methyl group.

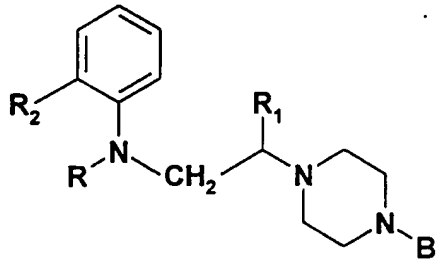
6. Any one of the following compounds:
1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-trifluoromethoxyphenyl)-2-aminoethyl]- 4-(2-methoxyphenyl)-piperazine,
1-[N-(2-trifluoromethoxyphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-phenoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-phenoxyphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-iodophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-iodophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-aminocarbonylphenyl)-2-aminoethyl]- 4-(2-methoxyphenyl)-piperazine,
1-[N-(2-cyanophenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-acetylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-2-aminoethyl]- 4-(4-indolyl)-piperazine,
1-[N-(2-nitrophenyl)-N-cyclohexanecarbonyl-2-aminoethyl]-4-(4-indolyl)-piperazine,
1-[N-(2-nitrophenyl)-2-aminoethyl)-4-(2,5-dichlorobenzyl)-piperazine,
1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2,5-dichlorobenzyl)-piperazine,
1-[N-(2-cyclohexylcarbonylaminocarbonylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-methoxycarbonylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-methoxycarbonylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-dimethylaminocarbonylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-methoxyphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine.

1-[N-(2-dimethylaminocarbonylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine
1-[N-(2-trifluoromethylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-methoxyphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-ethylaminocarbonylphenyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-ethylaminocarbonylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-trifluoromethylphenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-aminophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-acetylaminophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine N^1-oxide,
1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine N^4-oxide,
1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine N^1,N^4-dioxide,
1-[N-(2-nitrophenyl)-N-(3-furylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-(2-furylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-(2-thiophenecarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-(3-thiophenecarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-(4-pyridylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-(3-pyridylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-(2-pyrazinylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-(1-methylcyclohexylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-N-(1-phenylcyclohexylcarbonyl)-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-[2-(2,2,2-trifluoroethoxy)-phenyl]-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,

1-[N-[2-(2,2,2-trifluoroethoxy)-phenyl]-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-cyanophenyl)-N-cyclohexylcarbonyl-2-aminoethyl]-4-(2-methoxyphenyl)-piperazine,
1-[N-(2-nitrophenyl)-1-amino-2-propyl]-4-(2-methoxyphenyl)-piperazine, and
1-[N-(2-nitrophenyl)-N-cyclohexylcarbonyl-1-amino-2-propyl]-4-(2-methoxyphenyl)-piperazine;
or an enantiomer, N-oxide, hydrate or pharmaceutically acceptable salt of such a compound.

7. A pharmaceutical composition comprising a compound according to any preceding claim in admixture with a pharmaceutically acceptable diluent or carrier.

8. Use of a compound having the general formula I:



(I)

wherein
R represents a hydrogen atom or an alkylcarbonyl, a cycloalkylcarbonyl, substituted cycloalkylcarbonyl or monocyclic heteroarylcarbonyl group,
R_1 represents a hydrogen atom or a lower alkyl group,
R_2 represents a halogen atom or an alkoxy, phenoxy, nitro, cyano, acyl, amino, acylamino, alkylsulphonylamino, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, acylcarbamoyl, trifluoromethyl or polyfluoroalkoxy group, and
B represents a mono- or bicyclic aryl group, a substituted mono- or bicyclic aryl group, a mono- or bicyclic heteroaryl group, a substituted mono- or bicyclic heteroaryl group, a benzyl group or a substituted benzyl group,
or of an enantiomer, N-oxide, hydrate or pharmaceutically acceptable salt of such a compound, for the preparation of a medicament for the treatment of neuromuscular dysfunction of the lower urinary tract in a mammal.

9. Use according to claim 8 of a compound according to any of claims 1 to 6.

10. Use according to claim 8 or claim 9 for the preparation of a medicament which contains a pharmaceutically acceptable diluent or carrier.

11. Use according to any of claims 8 to 10 for the preparation of a medicament in a form suitable for oral administration.

12. Use according to claim 11 for the preparation of a medicament which contains from 50 to 400 mg of the compound in single dose form.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/04804

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D295/12 C07D307/68 C07D295/22 C07D333/38 C07D213/81
C07D213/82 C07D241/24 C07D209/08 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 04049 A (RECORDATI S.A.) 9 February 1995 see page 6; claims 1,6	1,7,8
X	US 3 472 854 A (S. ARCHER ET AL) 14 October 1969 cited in the application see example 1; table 1	1
X	US 4 205 173 A (B. V. SHETTY) 27 May 1980 cited in the application	1
A	see column 1, line 1 - column 2, line 10; claim 1; examples XXIII,XX,VII	7
X	GB 2 263 110 A (J. WYETH & BROTHER) 14 July 1993 cited in the application see claims 1,10,11	1,7,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 1998	13/01/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Voyiazoglou, D

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INTERNATIONAL SEARCH REPORT

Ir. ational Application No
PCT/EP 98/04804

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	O. E. FANCHER ET AL : "New analgesic N-substituted carboxamides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 7, 1964, pages 721-725, XP002087530 WASHINGTON US cited in the application see example 9; table I	1,7
A	M. ADACHI ET AL : "Aminohaloborane in organic synthesis. IX. Exclusive ortho acylation mreaction of N-monoaminoalkylamines" CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 33, no. 5, 2985, pages 1826-1835, XP002087531 TOKYO JP cited in the application see examples 16A,16B; table I	1
A	DE 24 05 441 A (SUMITOMO) 8 September 1974 cited in the application see claims 1,8	1,7
A	EP 0 711 757 A (F. HOFFMANN-LA ROCHE) 15 May 1996 cited in the application see claims 1,20,22	1,7,8

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

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Information on patent family members

Ir. ational Application No
PCT/EP 98/04804

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International Application No
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